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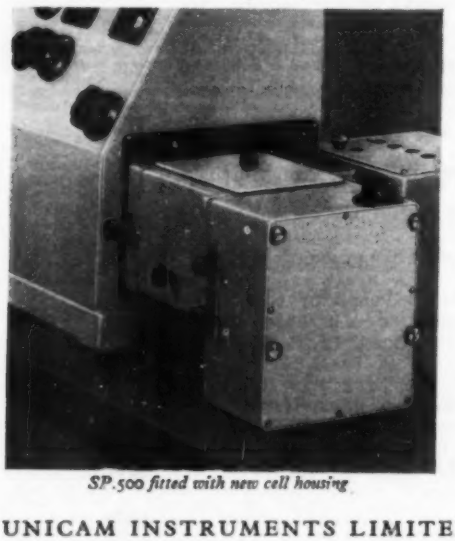

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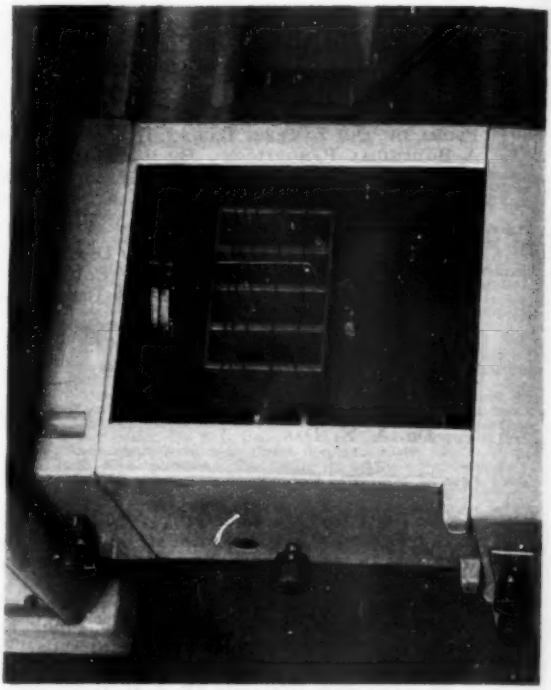

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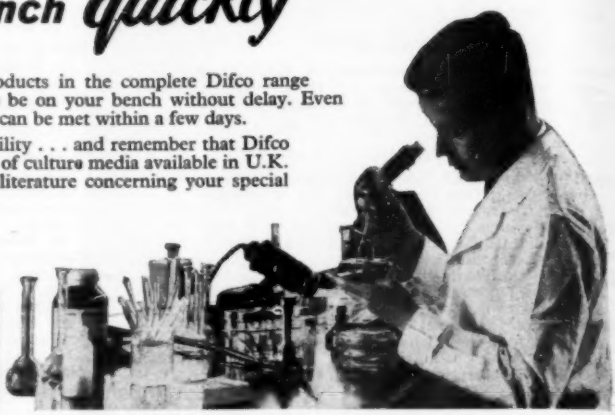

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POLITICS AND EDUCATION IN GHANA

RECENTLY, three Cabinet Ministers of Ghana—Mr. Adamafio, Minister of Information and Broadcasting; Mr. Duwuona-Hammond, Minister of Education; and Mr. Boateng, Minister of the Interior—have issued warnings to the students of Ghana's two Universities concerning their "arrogance and anti-State activities" which, so the Ministers declare, have been inherited "from a colonial past". We believe that anyone, student or otherwise, who indulges in serious anti-State activities should be warned and, if necessary, punished; but there is all the difference between anti-State activity and open opposition to the political policy of those in power—at any rate in a democracy. Moreover, to accuse the students, or anyone else, of arrogance strikes one as being somewhat naïve—even childish.

Recently, Osagyefo Dr. Kwame Nkrumah, President of the State of Ghana, was installed as Chancellor of the University of Ghana, near Accra, and on November 29 he was also installed as Chancellor of the Kwame Nkrumah University of Science and Technology at Kumasi. We understand there was an obvious lack of enthusiasm among the students during both these ceremonies, which angered the President. Though one cannot conceive of such resentment being demonstrated in such countries as the United States or Great Britain, the President's annoyance can be readily understood, though to appoint one and the same man as Chancellor of the only two Universities in a country is unique and risky, and in this case the objective seems very clear; it bodes ill for any semblance of autonomy in either University.

Wearing of academic gowns has been banned, and apparently stern measures, including the dismissal of some lecturers known to be "instilling in their students an attitude of disrespect for the President", are to be taken. The first policy strikes one as being absurd, and seems to be aimed against any attempt to follow the custom of many universities in the more highly developed countries. The second decision is more serious. Students are notoriously interested in politics, and are surely old enough to think for themselves, which is the very basis of a university education. It is a student's responsibility to think; but if as a result of such thinking he threatens to be a bad citizen, then he should be dealt with accordingly by his immediate superiors, that is, the university authorities and not those outside the university who enjoy political power.

All three Ministers have threatened that any students who "misbehave would be thrown out". This warning, too, should come from the university authorities and not from the State. This appears to be an intolerable position for any university, for it seems that those responsible for the running and development of the university are to be deprived of an important part of their academic responsibility. It should be they, and only they, who should take to task their students for breaches of university discipline (including, if necessary, expulsion) and not any outsider, not even a Minister of State.

The Minister of Information and Broadcasting in Ghana has announced that from now on the Council of the University of Science and Technology will be directed by the Government in the running of that institution so that the Government "might turn out men and women who have unflinching loyalty to the office and person of President Nkrumah". If this is to be taken literally, it savours too much of undesirable dictatorship. This alarming statement implies at least three conditions: (1) appointments to the staff must meet with the approval of the Government in power; (2) entry of students to that University will be conditional on (among other things) political grounds; (3) the University staff and their authority and the students will be subject to the whims and fancies of the Government.

There can be no autonomy in such an institution, no freedom of thought, expression and action, no development of democratic ideals. In fact, if the threats and warnings made by certain Ministers of State in Ghana are carried out, the University of Ghana, and certainly the University of Science and Technology, will not be universities at all.

On December 4, Mr. Duwuona-Hammond, the Minister of Education, addressed three hundred Ghana school teachers and told them that they must show loyalty to "the ideals of the State and of its chief architect, President Nkrumah". He proceeded to say: "Nobody resents fair comment, but systematic, spiteful and irresponsible criticism calculated to undermine the Government cannot be accepted as sincere teaching". The second statement would be acceptable to all educationists; but it will be understandable, in view of the first statement, if they suspect why it was made.

Ghana is an emergent country. It has fairly and justifiably won its independence. But it has yet much to learn, and during the past few decades the University of Ghana has been learning and developing with the help of academic men and women from the world's older universities—especially those of Great Britain. In Britain, the universities are proud of their autonomy and guard it with justifiable jealousy, though, in spite of the fact that they are increasingly dependent on State funds, they suffer no threat of State interference in the way they are conducted and the manner in which they train their students. Moreover, much to their credit, successive Governments have shown no tendency to influence the universities so far as policy is concerned. In fact, university students are encouraged to think for themselves, and, within reason, are entitled to their own political views and to express their opinions of Government and others in political power. Ghana would be wise to take note of this.

ELECTRON MICROSCOPY

Proceedings of the European Regional Conference on Electron Microscopy

Delft, 1960. Edited by A. L. Houwink and B. J. Spit. Vol. 1: Pp. i–xvi + 1–608. Vol. 2: Pp. xvii–xxvii + 609–1075. (Delft: Nederlandse Vereniging voor Electronenmicroscopie, 1961.) 135 florins the two volumes.

IT is very appropriate that the 1960 Regional Conference on Electron Microscopy should have been held at Delft, as was the first Conference in 1949. Delft is in a very real sense the birthplace of microscopy, and it is a fitting tribute to Antony von Leeuwenhoek, possibly the most acute of all microscopists, and a happy gesture that the covers of these two volumes should be impressed with an image of one of his microscopes. The twelve years which have elapsed since the first Conference have witnessed spectacular advances in this newer form of microscopy, both in technique and in the number of workers using the instrument. It could scarcely have been imagined, for example, that stemming from the first ultra-thin section demonstrated at Delft by Brettschneider in 1949, the use of sectioning for electron microscopy would by 1960 have become so routine a matter as to be in regular use in a multitude of electron microscope laboratories. Indeed, what impresses the reader of these volumes the most is both the range of materials which can be examined by this means and the extremely rapid, even explosive, burst of interest developed during these few years.

The books comprise reports of 246 articles presented at the Conference, copiously illustrated by electron micrographs. They are not therefore intended to be read, in the sense that text-books are read, but rather to be used as works of reference. The first volume, containing 138 articles, deals in the main with instrumentation, including an article on specimen techniques, with crystal physics and with metallurgical and other industrial applications. The second, of 108 articles, is devoted exclusively to biology. The leading article in Volume 1 deals with electron optics, leading naturally to a discussion of developments both in electron microscopes and in methods of use. The articles on solid-state physics (including crystal growth and lattice defects) are perhaps especially notable. In Volume 2 the cytology of muscle, skin, bone, sense organs, spermatozoids, and viruses all receive due attention. It is somewhat disappointing to see that while animal cytology is represented by a hundred articles, plant cytology accounts for only eight.

These two books together cover much of the field as explored in 1960. Even a cursory glance through the list of contents, however, reveals the absence of some names already famous in the field of electron microscopy and some lines of research, both well established and developing, which are not represented. This is clearly a fault neither of the organizers of the Conference nor of the editors, and explanation is surely to be sought on other and more fundamental lines. One contributory factor is that conferences on electron microscopy by their very nature meet only part of the needs of electron microscopists. Few workers are specifically interested in the instrument itself or even in their own electron micrographs alone. Rather are they interested in the results of electron microscopy as illuminating their own chosen fields and as contributing to the solution of problems often already stated before the advent of this new technique and of interest also to non-microscopists. They therefore both receive and confer more benefit by discussions in conferences arranged by their own professional bodies, before audiences acquainted with and sympathetic to their problems, than by reports to those with whom the only interest in common is the instrument itself. While it is clearly satisfactory to electron microscopists that they should form societies, and hold symposia which attract large numbers of articles, and while it is clearly desirable that electron microscopists should meet from time to time, it is not self-evident that the best interests of the separate sciences are achieved in this way.

The books are beautifully produced on excellent paper and the illustrations could in most cases scarcely have been better. Bibliographies are attached to each article, and each volume carries a complete author index. Both the publishers and the editors are to be complimented on this work. It is notable, moreover, that in these days of publication delays, the books have appeared in less than one year from the date of the Conference; it is not easy to see how this herculean task has been performed and the editors are to be highly commended on it.

Anyone who wishes to acquaint himself with the situation in electron microscopy up to 1960 could do no better than to read these two volumes.

R. D. Preston

FLORA OF THE ZAMBEZI BASIN

Flora Zambesiaca

Mozambique; Federation of Rhodesia and Nyasaland; Bechuanaland Protectorate, Vol. 1, Part 2. Edited by A. W. Exell and H. Wild. Pp. vi + 337–581. (London: Crown Agents for Oversea Governments and Administrations, 1961. Published on behalf of the Governments of Portugal, The Federation of Rhodesia and Nyasaland, and the United Kingdom.) 25*s*.

THE second part of the first volume of *Flora Zambesiaca* has made its welcome appearance. The part completes Volume 1, for which an index and title-page are provided. It covers the flowering plants from family 21, Caryophyllaceae to family 30, Sterculiaceae arranged in the Bentham and Hooker sequence. The joint editors are Mr. A. W. Exell of the British Museum (Natural History) and Dr. H. Wild of the Federal Herbarium, Salisbury, Southern Rhodesia. This part, as in the case of the first part, is an excellent example of botanical co-operation, for it contains contributions by botanists working at the British Museum (Natural History), the Federal Herbarium, Salisbury, Southern Rhodesia, the Botanical Laboratory of the Free University, Brussels, the National Herbarium, Pretoria, and the Royal Botanic Gardens, Kew, while the Portuguese Government is represented both on the Managing Committee and the editorial board of this Flora. The Flora covers the Federation of Rhodesia and Nyasaland, Mozambique and Bechuanaland Protectorate. The part under review contains accounts of 10 families, consisting of 55 genera and 265 species. The largest family is the Malvaceae with 16 genera and 111 species in the area, while the smallest is the Theaceae with one monotypic genus, *Ficalhoa*, alone. The plants included range from small annual herbs with inconspicuous flowers such as *Bergia* (in the Elatinaceae) to large

forest trees, 30 m. high, such as *Sterculia subviolacea* (in the Sterculiaceae), and the massive baobab, known scientifically as *Adansonia digitata* (in the Bombacaceae), so familiar to travellers in the drier parts of eastern and southern Africa.

The diagnostic keys, provided to distinguish the genera, species and in some cases the varieties, show signs of having been carefully prepared, and should be of great assistance to the user. The 46 plates, drawn by eight different artists, are of a high standard and add greatly to the helpfulness of the book, while the coloured frontispiece, depicting *Hibiscus rhodanthus*, is a pleasing addition.

The treatments adopted are in some cases interesting. The Hypericaceae merged with the tropical family Guttiferae will surprise botanists familiar with the temperate genus *Hypericum* alone. The placing of *Ficalhoa* in the Theaceae is now rather widely supported, as one has long felt unhappy about its being in the Ericaceae. The acceptance of the Illecebraceae as a family distinct from Caryophyllaceae shows how much the personal opinions of botanists enter into taxonomic decisions. Only recently, in another African regional Flora, these two families were treated as one.

At the generic level, *Hibiscus esculentus*, the young fruits of which are the well-known tropical vegetable okra, is placed in the genus *Abelmoschus*, while the tree widely spread throughout the area and hitherto known as *Thespesia garckeana* finds itself in the unfamiliar genus *Azanza*.

When one comes to species, one finds that a more conservative view has been taken, and a number of familiar names appear in synonymy. This tendency to accept a broader view of a species is very welcome and can at least partly be attributed to the taxonomists knowing the plants in the field and learning at first hand how greatly climatic, seasonal and edaphic conditions can modify them. It will undoubtedly make the Flora easier for the public to use.

The production is excellent, and the authors and editors are to be congratulated on the high standard of this much-needed work.

E. Milne-Redhead

A BOTANICAL PANOPTICON

A New Illustrated British Flora

By Dr. Roger W. Butcher. Part 1: Lycopodiaceae to Salicaceae. Pp. viii + 1016. (London: Leonard Hill (Books), Ltd., 1961.) 84s. net.

THERE was a time when every aspiring student of British plants first groped his way through "Bentham and Hooker" and then, with growing confidence, broached the more esoteric contents of "Butcher and Strudwick". The fact that it was generally considered unnecessary to mention the precise titles of either work was proof not only of the general popularity of the *Handbook of the British Flora* and *Further Illustrations of British Plants*, but also of the almost legendary fame of their respective authors. Dr. Butcher showed keen psychological insight in naming his book *Further Illustrations*, for, to be quite honest, most beginners and amateurs valued pictures more highly than text, and many professional botanists, now ageing and erudite, would, under pressure, confess that it was the genius of Walter Fitch and the urbane lucidity of Florence Strudwick, rather than the arid exactitudes of botanical prose, that guided their first steps along the rocky road of taxonomy.

Is the same true nowadays? Do young naturalists still turn to Fitch and Strudwick for assistance? Or has modern youth inherited such bumps of scientific understanding that it can imbibe Clapham, Tutin and Warburg as mother's milk and advance to erudition via chromosomes and histograms? I do not think so—nor evidently does Dr. Butcher—for his *New Illustrated British Flora* differs in no material respect from his earlier book on British plants. It is *Further Illustrations* expanded to include the entire range of native British phanerogams and vascular cryptogams, as well as many of the more widely established colonists, denizens and aliens. Almost the only concession to the 'new look' in British botany is the departure from the Bentham and Hooker sequence of families in favour of the Clapham, Tutin and Warburg scheme, and even here Dr. Butcher accepts the latest of phylogenetic vagaries with such ill-concealed reluctance that one wonders what irresistible forces compelled him to take this course.

The sad fact that Florence Strudwick did not live to prepare the illustrations for this new work has resulted in a loss of uniformity in the style and quality of the illustrations, though it should be added that at least two of the ten artists employed have attained Miss Strudwick's immaculate clarity and firmness of line, and that, on the whole, the 885 drawings in this first volume are perfectly satisfactory. The same, alas, cannot be said for the reproduction, perhaps in the case of those drawings transferred from *Further Illustrations* because the blocks have deteriorated with age, but less easily explained in other cases. Too many of the illustrations, at least in the review copy, are unduly black and murky, while a few are pallid to the point of anæmia. Something has surely gone wrong with *Equisetum hyemale* (Fig. 10) which, to judge from the scale, appears to be more slender than *E. trachyodon* (Fig. 11)—or should the illustrations be interchanged? The flowers of *Barbarea vulgaris* (Fig. 209) also appear considerably larger than those of *B. verna* (Fig. 212), which is neither in accordance with the facts nor with the accompanying legends.

Such minor slips and blemishes are, however, virtually inevitable in a detailed work of this magnitude. It is more general matters, such as the author's choice of subjects for inclusion in the volume, that are likely to intrigue the critics. Of course one recognizes the futility of wasting space on every fleeting casual and rubbish-tip waif that postures as a British plant, but it is difficult to follow the logic which admits *Hypericum canadense* and excludes *Cerastium brachypetalum*, which allows *Viola kitaibeliana* and disallows *Ranunculus muricatus*; and when one comes to scrutinize the so-called 'critical groups', even the most sanguine must begin to despair. Are there really ten species of *Thalictrum* in Britain—or for that matter six (or seven) *Cochlearias*? It would be unfair to expect Dr. Butcher to solve, at one blow, all the problems which have overtaxed the mental equipment of generations of taxonomists, but one cannot help feeling that if these, and a hundred similar problems in *Juniperus, Caltha, Erophila, Arabis, Viola, Polygala, Sagina, Salicornia*, etc., were to be given serious attention, not by one botanist, but by a group of botanists, prepared to follow up every possible clue, then elucidation would follow. Perhaps not, for it may be that our whole system of taxonomy and nomen-

clature is too crude and static to encompass the restless mutatings of living things, but at least the effort would be praiseworthy. Besides, it is demoralizing for any scientist to have to keep on repeating what he does not wholly believe.

It is sad to find that Dr. Butcher has joined forces with those who require a popular name for every unpopular plant: one senses political undertones in 'Red German Catchfly' (*Lychnis viscaria*), redressed perhaps by the fact that *Rumex orientalis* has escaped to become the 'Western Dock' and—it was bound to happen sooner or later—one blushes at the frankly clinical implications of Dickie's Bladder Fern. How fortunate that *Cystopteris dickieana* is such a very rare plant!

Finally, it must be pointed out that the Achlamydeae, Group VI (p. 37) in the mammoth identification key, do not have "both calyx and corolla present".

R. D. Meikle

THE MITES AND TONGUE-WORMS OF AFRICAN VERTEBRATES

The Arthropod Parasites of Vertebrates in Africa South of the Sahara, (Ethiopian Region)

Vol. 1 (Chelicerata). Edited by F. Zumpt. (Publications of the South African Institute for Medical Research, No. 1, Vol. 9.) Pp. vi+457. (Johannesburg: South African Institute for Medical Research, 1961.) R. 6.00.

THE "onlie begetter" of this handsome volume was undoubtedly the *Check List* of the late G. A. H. Bedford, published during 1927–36, a fact which is acknowledged in the first sentence of its introduction; it would perhaps have added a further touch of graciousness if it had been made clear that the very form of the present compilation is that inaugurated by Bedford—keys, figures, method of specific citation, sections, notes and even the general typography. Bedford's achievement was a great one, and to admit it to be so does not in the least diminish one's admiration for the extreme care and competence of all the authors of this, Bedford's successor.

Three decades of research in this field have increased the numerical total of Bedford's *Check List* many times and the present volume adds numerous new and excellent figures and completely new keys. The extreme care which has been taken by all the authors can be seen in the treatment of 'difficult' genera, for example, *Haemolaelaps*. A conservative systematics is evident everywhere, and if some acarologists feel that occasionally this conservative constraint may obscure some important relationships (as in some feather-mite genera), none, at least on the eastern side of the Atlantic, but will welcome the consequently rational treatment such as is accorded the Trombiculidae, in which family the fluidity of present-day generic concepts is frankly recognized and reflected.

The general introductory discussion of arthropod parasitism is succinct and reliable, and, within the obviously set limits which have been imposed, gives a useful survey of the subject for the purposes of the general student; but it leaves unanswered, of course, several problems such as why, for example, there are different patterns in the reduction of the biological cycle of the Acari. In this connexion it might be mentioned that the extremely complicated matter of the evolution of parasitism in the Trombidiformes is clearly if rapidly sketched, but one imagines that there will be several workers who will share my resistance to the suggestion that the Ereynetidae have evolved from "Trombicula-like" ancestors.

It seems ungrateful, given here so much, to ask more, but one could have wished for a system of cross-references between the bibliographical citations and the records. This would have made for easy validation of the latter, and although the specialist can perhaps often make an intelligent guess, the non-specialist has the labour of working systematically through all the entries. *Optat ephippia bos piger, optat arare caballus.*

F. A. Turk

FIFTY YEARS OF STEDMAN

Stedman's Medical Dictionary

Twentieth edition, completely revised. Pp. xlvii+1680+31 plates. (London: Baillière, Tindall and Cox, Ltd., 1961.) 110*s*.

ANY published work which has run into its twentieth edition has proved its worth. In 1911, Thomas Lathrop Stedman compiled the first edition of his medical dictionary which, compared with the latest, was relatively so simple that he needed no collaborators.

When the present work was projected, a team of experts in the various phases of medical lexicography was brought together to act not as advisory consultants but as working partners. These twenty-three consulting editors include such names as Prof. A. I. Lansing, C. D. Leake, and N. B. Taylor, and are supported by outstanding colleagues in the fields of dentistry and pharmacology. Together they have scrutinized each entry in the nineteenth edition, re-defined many thousands of them and inserted a vast number of new ones. Each entry carries with it, if necessary, a reference to the appropriate anatomical or pharmacological nomenclature, while tables are used for many sorts of entries, for example, methods, operations, diseases, anatomical structures and pharmacological terms.

One difference between this and other medical dictionaries is that it carries many dental terms; the volume will be equally useful to dental practitioners and students as to members of the medical profession. Many entries also relate to veterinary science. Obsolete words and expressions, duplications and repetitions have been eliminated while terms relating to botany, homœopathy, eclectic medicine, life insurance and electricity are also omitted unless they have medical applications.

Such wholesale alteration has meant a resetting of the entire work. The publishers have consequently used a new type face and arrangement which make the entries much easier to find and read. The pages are larger and there are many more of them. Pronunciations are given only where the editors consider English-speaking readers might have difficulties. With the vastly improved illustrations, the high-quality paper and the sturdy binding, *Stedman's Medical Dictionary* in its twentieth edition is so new that it resembles the first one only in bearing the name of Stedman. Although prepared in the United States, the producers had all English-speaking readers in mind during the production and the dictionary can be recommended to all who read English as remarkable value for money.

K. M. Hawkins

Handbuch der Papierchromatographie

Herausgegeben von I. M. Hais und K. Macek. Band 2: Bibliographie und Anwendungen. Pp. xxiv+726. (Jena: Gustav Fischer Verlag, 1960.) 44 D.M.

IN their introduction, the editors state that as it was difficult to incorporate a comprehensive bibliography on paper chromatography in their first volume on principles and techniques, they decided to do this separately in a second volume. This book contains more than 10,000 references (about four times as many as in Volume 1) and the arrangement follows roughly the same pattern as that of the subject-matter of the first volume. The references cover the period up to 1956; each is numbered and each title is given in full if the original language is English, French or German; otherwise the English or German translations as they occur in the recognized abstracts in these languages are given. The literature is covered very thoroughly, and there is probably no publication of any importance or interest about fundamentals or applications which has been missed. The systematic sectional arrangement, cross-references and comprehensive indexes of subjects and authors make for easy location of references to any desired topic in which paper chromatography has played a part.

R. CONSDEN

Précis de Climatologie

Par Prof. Ch. P. Péguy. Pp. iv+348+3 planches. (Paris: Masson et Cie., 1961.) Broché 42 N.F.; Cartonne toile 52 N.F.

THE studies on various aspects of physical geography and related sciences published since 1958 by Masson et Cie. have gained wide acceptance as soundly based, timely and authoritative: and the *Précis de Climatologie* maintains well the standards set by earlier volumes of the series. Prof. Péguy approaches his topic on a global scale, and is also actively concerned to demonstrate the practical applications of climate and weather to human and vegetal life. His method is first to discuss the elementary physical principles involved in climate: atmospheric radiation and circulation, temperature, humidity, and air mass characteristics; then to show the interrelations of these elements both on a local scale and for Earth as a whole; and next, to consider the effects of these elements on soils, and plant and animal life (especially human). Lastly, present-day theories are reviewed with, on occasion, evaluation by the author of differing approaches to a particular problem—for example, by Sorre and Köppen in the matter of thermal zones.

This treatment has the important advantage of subordinating theory and basic principles to interrelationships and effects within the natural environment; and thus Prof. Péguy's study is useful not only for geographers but also for the agronomist, botanist, planner and engineer concerned with problems of land development. Recent advances and trends within the subject can be treated at some length as a logical culmination: frontal and air-mass analysis; evapo-transpiration; rainfall dispersion, intensity, and efficacy; and the concept of water-budgets. There are also sections on climate classification and fluctuation.

With such an approach there can, however, be considerable risk of over-simplification and superficiality, especially when allied to a concise, near-didactic style of presentation. This the author in general avoids, due to extensive use of numerical examples, graphs, and a rigid statistical treatment of material. Too often in climatological treatises there is an insufficient factual basis—this is by no means the case here: although in one or two rare instances (for example, treatment of geostrophic forces and discussion of frontal surfaces) greater detail and clarity might have been attained. One might also have expected more than four pages on micro- and local-climates, especially in view of the exhaustive discussion of such matters as angle of incidence of the solar beam.

These, however, are very small matters when viewed alongside the many and solid merits of Prof. Péguy's work. Here in one volume we have a spread of modern climatological topics so far not brought together (at least in English), with a wide range of examples from the work of research workers both in Europe and America, completed in many instances by a review of future research possibilities. The work is a distinct advance in the subject, and is a demonstration of geographical techniques applied soundly to scientific material.

W. B. FISHER

Wunderwelt Kakteen

Von Curt Backeberg. Pp. 242 (176 Abbildungen). (Jena: Gustav Fischer Verlag, 1961.) 19.50 D.M.

THIS is one of the most entertaining books that the reviewer has read for a very long time. Dr. Backeberg is possibly the world's foremost authority on the classification of the Cactaceae and has published six large volumes on the taxonomy of the numerous species, magnificently illustrated and containing a wealth of critical judgment. But Dr. Backeberg is not concerned with taxonomy in the book that lies before us. Here we are introduced to the Cactaceae, not in the arid fashion of a botanical treatise, but most entertainingly to what he calls the "miracle world" of these extraordinary plants. The first miracle is how they manage to exist in some of the most arid and inhospitable parts of the Earth. The second miracle is the amazing variety of shape, size and characteristics developed. A glance at the family members shows that in size the species vary from huge specimens of several tons weight to minute marble-size prickly spheres; in shape they may be cylindrical, spherical, erect, simple or branched; the surface may be smooth, wavy or furrowed, with or without a fearsome armament of spines; the flowers, whether large or small, night- or day-flowering, are, by any standards, beautiful; the flesh of some species yields food and drink, and the notorious drug mescalin can be obtained from another.

Many additional uses are mentioned, one macabre, some utilitarian, some humorous. The Aztecs slaughtered their human sacrifices on a bed made from the cut stems of one of the larger specimens. The frame-work of a hut can be made from the stems of other species. "Cactus fiends" in California decorate their clothing with cacti while "Miss Cactus" wears a spiny crown. These prickly plants are a boon to the caricaturist, for the man who sat down on a cactus can scarcely fail to raise a smile. Romanticists have even written poetry about them, and such is their attraction that "out and out" fiends will even descend to barefaced theft to acquire a rare specimen.

The book is beautifully illustrated, beautifully printed, a credit to Dr. Backeberg and, let us add, worthy of the Cactaceae.

N. L. BOR

XUM

SMITHSON TENNANT, 1761-1815

By Dr. A. E. WALES
Principal, Burnley Municipal College

SMITHSON TENNANT was born at Selby, Yorkshire, on November 30, 1761, and christened in the Abbey Church there on December 3. His father, the Rev. Calvert Tennant, was the younger son of Edward Tennant of Mount Parke Farm, Wensley, and a Fellow of St. John's College, Cambridge. His mother was Mary, the only surviving daughter of William Daunt, apothecary of Selby. The Rev. Calvert Tennant's sister, Alice, married George Dinsdale of Nappa Hall, Wensleydale, and her daughter Alice married Christopher Pryme of Hull. The son of this marriage was George Pryme (1781–1868), who held the professorship of political economy at Cambridge, while Tennant was the professor of chemistry there (1813–15).

Tennant lost his father when he was ten years old, and his mother, by a fall from her horse while they were out riding in 1781, when he was twenty. During the intervening period, he attended the grammar schools of Scorton, Tadcaster and Beverley, in all of which he was fortunate to come under the influence of progressive and enlightened headmasters. It was during this period that the foundations of his later life as a natural philosopher were laid, for in addition to a good grounding in the classics, mathematics and French, the early interest in science which resulted from studying his grandfather Daunt's books was further encouraged by attendance in Tadcaster at the lecture of a Mr. Walker, an itinerant lecturer on popular science, and by the full use which he made of the excellent library at Beverley Grammar School, in which he found and eagerly studied a copy of Newton's *Treatise on Optics*.

His mother encouraged his growing love for science, and in 1781 plans were made for him to live as a pupil with Joseph Priestley. These, however, fell through and instead, just after his mother's fatal accident, Tennant entered the University of Edinburgh ostensibly as a medical student, but in reality so that he could study chemistry under Black. His notebooks of Black's lectures on chemistry, those of Munro Secundus on anatomy and surgery, and of Walker on natural history are still in existence. At Edinburgh, Tennant came into intimate relationship not only with Black but also with Hutton the geologist, Playfair the mathematician and Webb Seymour and his friends, the Horners, and it may be that Tennant performed experiments under the direction of Black and Hutton designed to support the latter's theory of rock formation. Tennant's stay in Edinburgh and especially his close association with Black profoundly influenced his attitude to science, confirming him in his choice of chemistry as the sphere of his life's work and leading him to accompany Black about 1790 as among the very first British scientists to accept in full the implications of the antiphlogistic theory.

Tennant left Edinburgh in 1781 and entered the University of Cambridge, again as a medical student, first as a pensioner at Christ's College and then, in 1782, as a Fellow Commoner of Emmanuel College. In an age when Fellow Commoners were noted more for their profligacy than for studious habits, Tennant's dedication to the pursuit of scientific inquiry is outstanding, especially as he was now in complete control of his own fortunes. Tennant's close friends at Cambridge included Sir Busick Harwood, who occupied the chair of anatomy during 1785–1814 and was Downing professor of medicine during 1800–14; Isaac Milner, who became the first Jacksonian professor in 1793 and to whom Tennant lent his notes of Black's lectures on chemistry, Dr. Edward Waring, the Lucasian professor of mathematics, Whitehall Whitehall Davies, a close family friend of his boyhood; Thomas Smith, later of Easton Grey and friend of Ricardo and Malthus and John Whishaw, later the "Pope of Holland House", confidant of the most influential of Whig politicians and Tennant's lifelong correspondent. Both Milner and Waring sponsored his election to the fellowship of the Royal Society in 1785 when he was twenty-four, and all of them remained his close friends throughout his life. In 1788, he "kept his Acts" for the degree of M.B., and a historian of the period who knew him in College remarks that this Act and that for his M.D. in 1796 were "of the highest order though marked by great eccentricity".

In addition to his preoccupation with items of chemical research, Tennant, while at Cambridge, began his foreign travels. In 1784 he visited Denmark and Sweden with the object of becoming personally acquainted with Scheele, Gahn and Berzelius. The visit stimulated his interest in geology and mineralogy, especially as he learnt from Gahn the use of the blowpipe in mineral analysis and soon became an acknowledged expert. In 1786 he paid a visit to France, Holland and the Lowlands, where he met Berthollet, Delametherie and very probably Lavoisier. This tour enlarged and deepened his interest in political economy, a subject which fascinated him for the rest of his life. A further European tour in 1793 took him to Switzerland, where he met Gibbon, then living out his last years at Lausanne. Returning via Italy, Germany and France, he remarked that most of the German chemists he had met appeared still to be preoccupied with the search for the 'philosopher's stone'. About this time, Tennant was asked to stand as a candidate for the Jacksonian professorship at Cambridge, but withdrew his name later. F. J. H. Wollaston was eventually elected.

Shortly after taking his degree in 1788, Tennant left Cambridge to reside in London at 4, Garden Court, Temple, and began to engage in chemical research, to attend meetings of learned societies and to build up a wider and wider circle of friends and acquaintances among the scientists, political economists and political reformers of the day. He never practised medicine, although he seems to have been very much attracted to the works and opinions of Sydenham and the chemical aspects of disease. His personal fortune, his love of independence and hatred of restraint, his sensitive nature and benevolent personality stifled in him any desire to undertake the drudgery of the life of a practising physician, and added to this there was the growing success attending his private researches. Between 1791 and 1797 he read papers before the Royal Society

on the decomposition of fixed air, the nature of diamond and the action of nitre on gold and platina, all showing his growing mastery of research methods and in concept and design and showing, too, the strong influences of Black and the Edinburgh school of chemistry, the new ideas of chemical philosophy originating in the French school under Lavoisier and bearing, within the results, the seeds of greater triumphs in the future.

At this period of his life, Tennant's situation was indeed an enviable one. Rich enough to follow his own inclinations, he was at peace with himself because of his decision to devote himself to chemical research, was well established in London as a scientist of repute, and by the charm and benevolence of his personality was the centre of a widening circle of intellectual and influential friends. John Whishaw had come to live near him and through his friendship Tennant moved among the members of the Whig party at Holland House, while Francis Horner lived very near him in the Temple. The only ill-fortune was a gradual decline in his health, and even this turned out for the best, for, on being urged to cultivate more interests, he took up horse riding, in which he had not indulged since his mother's tragic death. This new form of exercise, which he continued to practise for the rest of his life, not only restored his health, but also started him off on a new venture. He became so interested in farming that, after experimenting for a year or two with a few acres of land near Epworth in Lincolnshire, he purchased 500 acres of land newly allocated under the Enclosure Act at Shipham in Somerset. On this land, Tennant built a small country house in which he lived every summer and entertained his friends. His interest in farming was not in growing crops, but in conducting agricultural experiments, and his experiences led to the publication of his paper on the different sorts of lime used in agriculture with special reference to the deleterious effect on crops of magnesium limestone.

So, from about 1800 onwards, Tennant's life moved within two circles, each with its own friends and acquaintances but at times overlapping; one predominantly scientific and the other centred around politics and political economy. The latter included Thomas Smith, and his home at Easton Grey in Wiltshire, which was within easy travelling distance of Tennant's country house. He was a constant visitor at Easton Grey, where he was held in the greatest personal esteem and where he became friendly with Ricardo and Malthus. The political circle also included Whishaw, Warburton, Sharp, Rogers, Dumont, Sir Samuel Romilly, Sir J. Mackintosh, Lord Brougham and Francis Horner, and others who moved among the Whigs of Holland House and belonged to a select dining club called the 'King of Clubs'. Here the talk was of reform and theories of political economy, and Tennant's interest was so aroused that he offered to found a chair of political economy at Cambridge and contemplated writing a treatise which would embody his views on the subject with reference both to Britain and to other European countries.

This increasing preoccupation with political economy and reform did not, however, affect in any way his scientific activities. His paper on the composition of emery published in 1802 gives evidence of his continuing experimental work, but a more important feature of his scientific life is the deepening of his friendship with W. H. Wollaston, which blossomed into active collaboration and partnership during the next ten years. The friendship between the two men began at Cambridge, where Wollaston was a Pensioner and Scholar at Gonville and Caius College from 1782, graduating M.B. in 1787. He, too, attended Milner's lectures on chemistry and was taught the use of the blowpipe in mineral analysis by Tennant himself. During 1787–97 Wollaston was practising medicine in Huntingdon and Bury St. Edmunds, but when he went to London permanently in 1797, in order to pursue the calling of physician, the friendship was renewed and became intimate enough for Wollaston to act as Tennant's assistant during his experiments on the analysis of the diamond in 1797. It may be that this fruitful collaboration was a real factor, as well as the well-known incident at St. George's Hospital, in influencing Wollaston in his decision to give up a career in medicine for one devoted to chemical research. Indeed, there is evidence that Tennant's influence on Wollaston at this period of his life was very profound, for Warburton wrote in his biography of Wollaston that "Wollaston held Tennant's knowledge of the sciences in profound admiration and a few years after this time expressed his despair of ever becoming Tennant's equal as a Chemist".

From at least 1800 until his death in 1815, Tennant was both a financial and a scientific partner of Wollaston, a collaboration which brought fame to both men and success in many spheres of scientific achievement. The most spectacular result of the collaboration was achieved by the successful outcome of the series of experiments, initiated by a further study of Tennant's paper on the action of nitre on platina, which resulted in Tennant's discovery and extraction of osmium and iridium from crude platina, and Wollaston's discovery and extraction of palladium and rhodium. For this discovery Tennant was awarded the Copley Medal of the Royal Society, and Wollaston went on to develop his well-known method of producing malleable platinum and so pure platinum sheet. There is some evidence to suggest that this method may have owed something to Tennant's friendship with Black at Edinburgh. The practical result, however, was that the two men proceeded to make and sell the first platinum stills for use in the manufacture and purification of sulphuric acid. A further successful venture which lasted until 1811 was the manufacture of oxalic acid and oxalates, tartaric and citric acids from argol and lemon juice.

To this partnership, Tennant contributed money, a wealth of scientific acumen and knowledge and some practical skill, but it was Wollaston who contributed more and more of all three as time went on. Indeed, during the partnership, Tennant began increasingly to show something of that trait in his character on which all his friends have commented—the exhibition of a sense of a lack of purpose, a carelessness sometimes amounting almost to indolence which seemed to take possession of him and seemed to them to be akin to that shown by Dr. Black himself. The friendship, however, remained firm and close, because Tennant and Wollaston visited Ireland together in 1805. Tennant repeated the visit in 1806, but this time with W. G. Browne, the celebrated African traveller and explorer, another whose friendship Tennant valued highly until Browne's assassination near Tabriz in 1813. This friendship led to a similar one with the explorer Burkhardt, who died in 1809.

In addition to being a Fellow of the Royal Society and a member of the Royal Institution, Tennant was a founder member of the Askesian Society (1799),

renamed the Geological Society in 1806. In 1811, Tennant contributed a short note to the Society on native concrete boracic acid, and in 1813, when he was a vice-president, he delivered a lecture to the Society on the principles of mineralogy, in which he expressed his great indebtedness to the views expressed by Berzelius, who had stayed with him at his farm in 1812.

The success of this lecture, and those which Tennant was accustomed to give on chemistry and mineralogy to quite large gatherings of his friends in his rooms at Garden Court, together with his outstanding scientific achievements, convinced his friends of his suitability as a candidate for the professorship of chemistry at Cambridge, and in 1813 he was elected to the chair, following Farish, who had been elected to the Jacksonian professorship.

During the remaining two years of his life, Tennant divided his time between Cambridge, London and his farm at Shipham. Letters in existence show a ripening friendship between Tennant and Berzelius after the latter's visit to England in 1812, and they throw light, too, on his friendship with the scientists Thomas Young, Marcet, Dr. McMichael and Sir James Sebright.

Tennant was involved in an interesting experience which may have had later important repercussions. An explosion occurred in a gas-holder belonging to the Gas Light Co. in 1813. In 1814, a committee from the Royal Society was charged with investigating the matter; and Tennant, who was a member of the Council of the Society, and another (Wollaston ?), after a great deal of experimental work, showed that a flame will not pass through thin tubes and ignite an explosive mixture. Davy repeated these experiments in the following year and from the results discovered the use of gauze in the manufacture of the safety lamp. Dr. Marcet, writing to Berzelius in 1816, implies that Davy knew of Tennant's previous work but Davy always denied this.

Tennant's election as professor of chemistry at Cambridge gave great satisfaction to all concerned and had a stimulating effect on Tennant himself. Because of his scientific reputation and ability, and his personal qualities, it was confidently expected that he would establish and build up a notable school of chemistry in the University, and, but for his untimely death, there is every reason to think that this would have happened. His first course of lectures was attended by large audiences who were entertained and instructed by a masterly exposition of chemical principles illustrated by many experiments both of his own devising and also supplied by his many scientific friends. Among his first students were Charles Babbage and J. W. H. Herschel. During his short tenure of the professorship, Tennant revived an old interest in galvanism and built a much-improved voltaic battery embodying several unique features which he used with great success in his lectures. He also developed a new method of manufacturing potassium and published the results of his very first piece of experimental research on double distillation. It is now known that on the eve of his last Continental tour in 1814 he had completed two further pieces of research, one on the use of oxalic acid in the formation of sugar from starch and the other on the existence, extraction and purification of iodine from marine sources. He had also come to the conclusion that aragonite and calcite were dimorphic states of calcium carbonate, and he contemplated the publication of what would have been an important step in crystallography.

In September 1814 Tennant sailed for France, with Marcet and Wollaston, to enjoy a Continental holiday. After touring southern France, meeting Berthollet and Berard in Marseilles and staying with scientific friends in Paris, he reached Boulogne on his way home on February 22, 1815. Strong winds prevented a boat from leaving the harbour and Tennant, accompanied by Baron Bulow, went riding on the sands. While inspecting a small fort, a bridge over a deep ditch gave way under Tennant's horse, and as a result of this accident Tennant died in Boulogne hospital and was buried in Boulogne cemetery.

So far as is known, no likeness of Tennant exists, but it is said that in his features he closely resembled the philosopher Locke. He never married and seemed quite indifferent to female society. Of his influence on the scientific events of his day, there can be no doubt of its prime importance, not only because of his own personal contributions, but also because of his influence on the work of other scientists, notably Davy and Wollaston—an influence which does not seem to have been adequately recognized or appreciated. Of his character and personality, some words written by Brande and some by Dyer may be quoted. Brande wrote in his *Manual of Chemistry*: "Mr. Smithson Tennant was a profound philosopher and a matchless companion. His learning was without pedantry, and his wit without sarcasm. He was deep but always clear, gentle but never dull. To those who knew him not, it is scarcely possible to offer an adequate representation of his singularly pleasing and enlightened character by those who enjoyed his acquaintance and partook of his social hours. His extent of knowledge, his happy and unrivalled talent for conversation, his harmless but brilliant flashes of merriment and all his amiable peculiarities can never be forgotten". Dyer, who knew him at Cambridge, wrote: "It is pleasing to pay respect to a person whose modesty surpassed his industry, whose love of science was greater than his love of fame and to whom nothing perhaps was wanting to have rendered him one of the most distinguished men of his time except better health and more systematic habits of study".

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GENERAL NATURE OF THE GENETIC CODE FOR PROTEINS

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THERE is now a mass of indirect evidence which suggests that the amino-acid sequence along the polypeptide chain of a protein is determined by the sequence of the bases along some particular part of the nucleic acid of the genetic material. Since there are twenty common amino-acids found throughout Nature, but only four common bases, it has often been surmised that the sequence of the four bases is in some way a code for the sequence of the amino-acids. In this article we report genetic experiments which, together with the work of others, suggest that the genetic code is of the following general type:

(*a*) A group of three bases (or, less likely, a multiple of three bases) codes one amino-acid.

(*b*) The code is not of the overlapping type (see Fig. 1).

(*c*) The sequence of the bases is read from a fixed starting point. This determines how the long sequences of bases are to be correctly read off as triplets. There are no special 'commas' to show how to select the right triplets. If the starting point is displaced by one base, then the reading into triplets is displaced, and thus becomes incorrect.

(*d*) The code is probably 'degenerate'; that is, in general, one particular amino-acid can be coded by one of several triplets of bases.

The Reading of the Code

The evidence that the genetic code is not overlapping (see Fig. 1) does not come from our work, but from that of Wittmann[1] and of Tsugita and Fraenkel-Conrat[2] on the mutants of tobacco mosaic virus produced by nitrous acid. In an overlapping triplet code, an alteration to one base will in general change three adjacent amino-acids in the polypeptide chain. Their work on the alterations produced in the protein of the virus show that usually only one amino-acid at a time is changed as a result of treating the ribonucleic acid (RNA) of the virus with nitrous acid. In the rarer cases where two amino-acids are altered (owing presumably to two separate deaminations by the nitrous acid on one piece of RNA), the altered amino-acids are not in adjacent positions in the polypeptide chain.

Brenner[3] had previously shown that, if the code were universal (that is, the same throughout Nature), then all overlapping triplet codes were impossible. Moreover, all the abnormal human hæmoglobins studied in detail[4] show only single amino-acid changes. The newer experimental results essentially rule out all simple codes of the overlapping type.

If the code is not overlapping, then there must be some arrangement to show how to select the correct triplets (or quadruplets, or whatever it may be) along the continuous sequence of bases. One obvious suggestion is that, say, every fourth base is a 'comma'. Another idea is that certain triplets make 'sense', whereas others make 'nonsense', as in the comma-free codes of Crick, Griffith and Orgel[5]. Alternatively, the correct choice may be made by starting at a fixed point and working along the sequence of bases three (or four, or whatever) at a time. It is this possibility which we now favour.

Experimental Results

Our genetic experiments have been carried out on the *B* cistron of the r_{II} region of the bacteriophage *T4*, which attacks strains of *Escherichia coli*. This is the system so brilliantly exploited by Benzer[6,7]. The r_{II} region consists of two adjacent genes, or 'cistrons', called cistron *A* and cistron *B*. The wild-type phage will grow on both *E. coli B* (here called *B*) and on *E. coli K*12 (λ) (here called *K*), but a phage which has lost the function of either gene will not grow on *K*. Such a phage produces an *r* plaque on *B*. Many point mutations of the genes are known which behave in this way. Deletions of part of the region are also found. Other mutations, known as 'leaky', show partial function; that is, they will grow on *K* but their plaque-type on *B* is not truly wild. We report here our work on the mutant *P* 13 (now re-named *FC* 0) in the *B*1 segment of the *B* cistron. This mutant was originally produced by the action of proflavin[8].

We[9] have previously argued that acridines such as proflavin act as mutagens because they add or delete a base or bases. The most striking evidence in favour of this is that mutants produced by acridines are seldom 'leaky'; they are almost always completely lacking in the function of the gene. Since our note was published, experimental data from two sources have been added to our previous evidence: (1) we have examined a set of 126 r_{II} mutants made with acridine yellow; of these only 6 are leaky (typically about half the mutants made with base analogues are leaky); (2) Streisinger[10] has found that whereas mutants of the lysozyme of phage *T4* produced by base-analogues are usually leaky, all lysozyme mutants produced by proflavin are negative, that is, the function is completely lacking.

If an acridine mutant is produced by, say, adding a base, it should revert to 'wild-type' by deleting a base. Our work on revertants of *FC* 0 shows that it usually

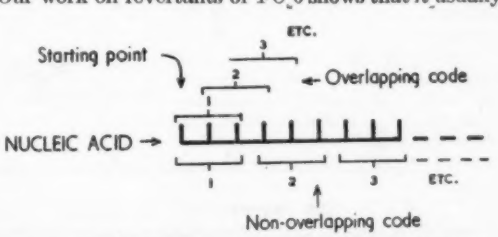

Fig. 1. To show the difference between an overlapping code and a non-overlapping code. The short vertical lines represent the bases of the nucleic acid. The case illustrated is for a triplet code

reverts not by reversing the original mutation but by producing a second mutation at a nearby point on the genetic map. That is, by a 'suppressor' in the same gene. In one case (or possibly two cases) it may have reverted back to true wild, but in at least 18 other cases the 'wild type' produced was really a double mutant with a 'wild' phenotype. Other workers[11] have found a similar phenomenon with r_{II} mutants, and Jinks[12] has made a detailed analysis of suppressors in the h_{III} gene.

The genetic map of these 18 suppressors of *FC* 0 is shown in Fig. 2, line *a*. It will be seen that they all fall in the *B*1 segment of the gene, though not all of them are very close to *FC* 0. They scatter over a region about, say, one-tenth the size of the *B* cistron. Not all are at different sites. We have found eight sites in all, but most of them fall into or near two close clusters of sites.

In all cases the suppressor was a non-leaky *r*. That is, it gave an *r* plaque on *B* and would not grow on *K*. This is the phenotype shown by a complete deletion of the gene, and shows that the function is lacking. The only possible exception was one case where the suppressor appeared to back-mutate so fast that we could not study it.

Each suppressor, as we have said, fails to grow on *K*. Reversion of each can therefore be studied by the same procedure used for *FC* 0. In a few cases these mutants apparently revert to the original wild-type, but usually they revert by forming a double mutant. Fig. 2, lines *b*–*g*, shows the mutants produced as suppressors of these suppressors. Again all these new suppressors are non-leaky *r* mutants, and all map within the *B*1 segment for one site in the *B*2 segment.

Once again we have repeated the process on two of the new suppressors, with the same general results, as shown in Fig. 2, lines *i* and *j*.

All these mutants, except the original *FC* 0, occurred spontaneously. We have, however, produced one set (as suppressors of *FC* 7) using acridine yellow as a mutagen. The spectrum of suppressors we get (see Fig. 2, line *h*) is crudely similar to the spontaneous spectrum, and all the mutants are non-leaky *r*'s. We have also tested a (small) selection of all our mutants and shown that their reversion-rates are increased by acridine yellow.

Thus in all we have about eighty independent *r* mutants, all suppressors of *FC* 0, or suppressors of suppressors, or suppressors of suppressors of suppressors. They all fall within a limited region of the gene and they are all non-leaky *r* mutants.

The double mutants (which contain a mutation plus its suppressor) which plate on *K* have a variety of plaque types on *B*. Some are indistinguishable from wild, some can be distinguished from wild with difficulty, while others are easily distinguishable and produce plaques rather like *r*.

We have checked in a few cases that the phenomenon is quite distinct from 'complementation', since the two mutants which separately are phenotypically *r*, and together are wild or pseudo-wild,

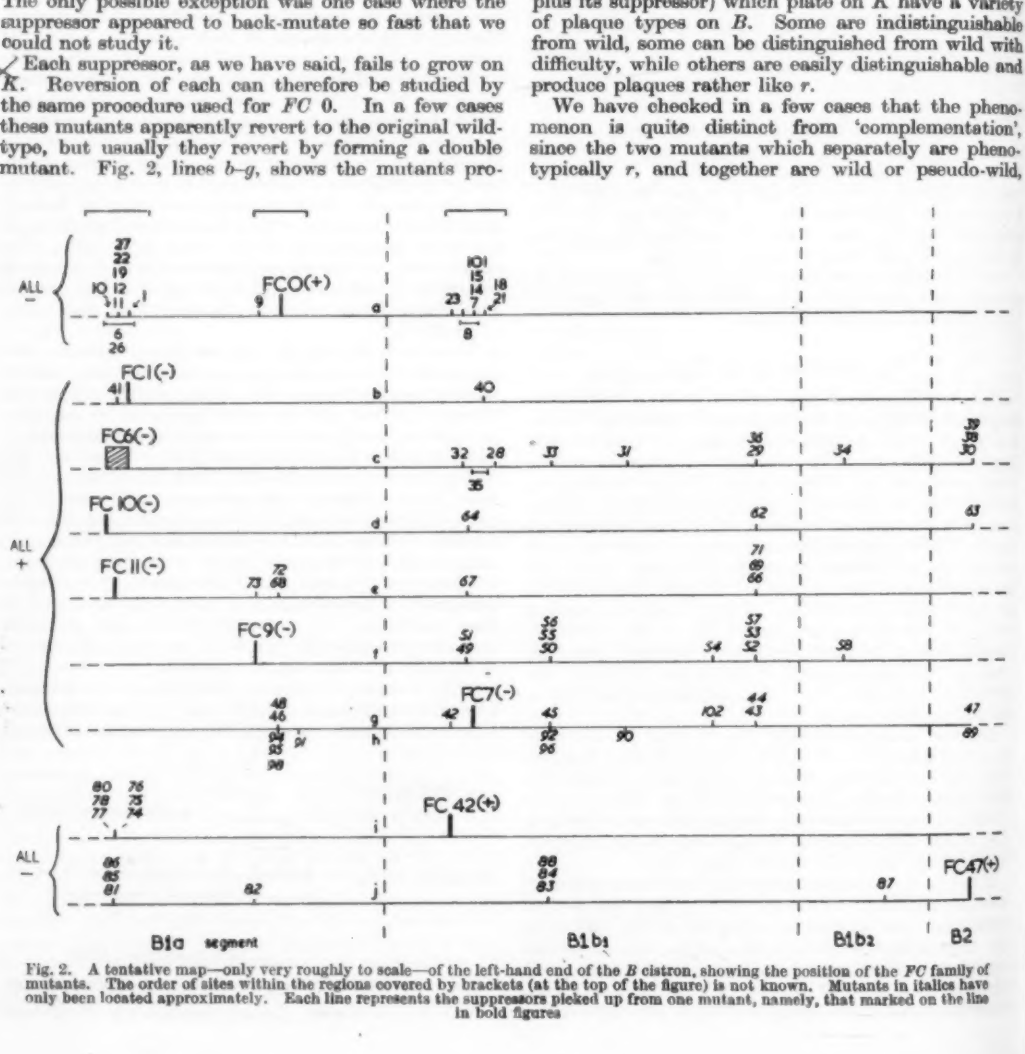

Fig. 2. A tentative map—only very roughly to scale—of the left-hand end of the *B* cistron, showing the position of the *FC* family of mutants. The order of sites within the regions covered by brackets (at the top of the figure) is not known. Mutants in italics have only been located approximately. Each line represents the suppressors picked up from one mutant, namely, that marked on the line in bold figures

must be put together in the same piece of genetic material. A simultaneous infection of *K* by the two mutants in separate viruses will not do.

The Explanation in Outline

Our explanation of all these facts is based on the theory set out at the beginning of this article. Although we have no direct evidence that the *B* cistron produces a polypeptide chain (probably through an RNA intermediate), in what follows we shall assume this to be so. To fix ideas, we imagine that the string of nucleotide bases is read, triplet by triplet, from a starting point on the left of the *B* cistron. We now suppose that, for example, the mutant *FC* 0 was produced by the insertion of an additional base in the wild-type sequence. Then this addition of a base at the *FC* 0 site will mean that the reading of all the triplets to the right of *FC* 0 will be shifted along one base, and will therefore be incorrect. Thus the amino-acid sequence of the protein which the *B* cistron is presumed to produce will be completely altered from that point onwards. This explains why the function of the gene is lacking. To simplify the explanation, we now postulate that a suppressor of *FC* 0 (for example, *FC* 1) is formed by deleting a base. Thus when the *FC* 1 mutation is present by itself, all triplets to the right of *FC* 1 will be read incorrectly and thus the function will be absent. However, when both mutations are present in the same piece of DNA, as in the pseudo-wild double mutant *FC* (0 + 1), then although the reading of triplets between *FC* 0 and *FC* 1 will be altered, the original reading will be restored to the rest of the gene. This could explain why such double mutants do not always have a true wild phenotype but are often pseudo-wild, since on our theory a small length of their amino-acid sequence is different from that of the wild-type.

For convenience we have designated our original mutant *FC* 0 by the symbol + (this choice is a pure convention at this stage) which we have so far considered as the addition of a single base. The suppressors of *FC* 0 have therefore been designated −. The suppressors of these suppressors have in the same way been labelled as +, and the suppressors of these last sets have again been labelled − (see Fig. 2).

Double Mutants

We can now ask: What is the character of any double mutant we like to form by putting together in the same gene any pair of mutants from our set of about eighty? Obviously, in some cases we already know the answer, since some combinations of a + with a − were formed in order to isolate the mutants. But, by definition, no pair consisting of one + with another + has been obtained in this way, and there are many combinations of + with − not so far tested.

Now our theory clearly predicts that all combinations of the type + with + (or − with −) should give an *r* phenotype and not plate on *K*. We have put together 14 such pairs of mutants in the cases listed in Table 1 and found this prediction confirmed.

Table 1. DOUBLE MUTANTS HAVING THE *r* PHENOTYPE

− With −	+ With +	
FC (1 + 21)	*FC* (0 + 58)	*FC* (40 + 57)
FC (23 + 21)	*FC* (0 + 38)	*FC* (40 + 58)
FC (1 + 23)	*FC* (0 + 40)	*FC* (40 + 55)
FC (1 + 9)	*FC* (0 + 55)	*FC* (40 + 54)
	FC (0 + 54)	*FC* (40 + 38)

At first sight one would expect that all combinations of the type (+ with −) would be wild or pseudo-wild, but the situation is a little more intricate than that, and must be considered more closely. This springs from the obvious fact that if the code is made of triplets, any long sequence of bases can be read correctly in one way, but incorrectly (by starting at the wrong point) in two different ways, depending whether the 'reading frame' is shifted one place to the right or one place to the left.

If we symbolize a shift, by one place, of the reading frame in one direction by → and in the opposite direction by ←, then we can establish the convention that our + is always at the head of the arrow, and our − at the tail. This is illustrated in Fig. 3.

We must now ask: Why do our suppressors not extend over the whole of the gene? The simplest postulate to make is that the shift of the reading frame produces some triplets the reading of which is 'unacceptable'; for example, they may be 'nonsense', or stand for 'end the chain', or be unacceptable in some other way due to the complications of protein structure. This means that a suppressor of, say, *FC* 0 must be within a region such that no 'unacceptable' triplet is produced by the shift in the reading frame between *FC* 0 and its suppressor. But, clearly, since for any sequence there are *two* possible misreadings, we might expect that the 'unacceptable' triplets produced by a → shift would occur in different places on the map from those produced by a ← shift.

Examination of the spectra of suppressors (in each case putting in the arrows → or ←) suggests that while the → shift is acceptable anywhere within our region (though not outside it) the shift ←, starting from points near *FC* 0, is acceptable over only a more limited stretch. This is shown in Fig. 4. Somewhere in the left part of our region, between *FC* 0 or *FC* 9 and the *FC* 1 group, there must be one or more unacceptable triplets when a ← shift is made; similarly for

Fig. 3. To show that our convention for arrows is consistent. The letters *A*, *B* and *C* each represent a different base of the nucleic acid. For simplicity a repeating sequence of bases, *ABC*, is shown. (This would code for a polypeptide for which every amino-acid was the same.) A triplet code is assumed. The dotted lines represent the imaginary 'reading frame' implying that the sequence is read in sets of three starting on the left

the region to the right of the *FC* 21 cluster. Thus we predict that a combination of a + with a − will be wild or pseudo-wild if it involves a → shift, but that such pairs involving a ← shift will be phenotypically *r* if the arrow crosses one or more of the forbidden places, since then an unacceptable triplet will be produced.

Table 2. Double Mutants of the Type (+ with −)

− \ +	*FC* 41	*FC* 0	*FC* 40	*FC* 42	*FC* 58 *	*FC* 63	*FC* 38
FC 1	*W*	*W*	*W*		W		W
FC 86		W	W	W	W	W	
FC 9	*r*	*W*	W	W	*W*		W
FC 82	*r*		W	W	W	W	
FC 21	*r*	*W*			W		W
FC 88	*r*	*r*			W	W	
FC 87	*r*	*r*	*r*	*r*			W

W, wild or pseudo-wild phenotype; *W*, wild or pseudo-wild combination used to isolate the suppressor; *r*, *r* phenotype.
* Double mutants formed with *FC* 58 (or with *FC* 34) give sharp plaques on *K*.

We have tested this prediction in the 28 cases shown in Table 2. We expected 19 of these to be wild, or pseudo-wild, and 9 of them to have the *r* phenotype. In all cases our prediction was correct. We regard this as a striking confirmation of our theory. It may be of interest that the theory was constructed before these particular experimental results were obtained.

Rigorous Statement of the Theory

So far we have spoken as if the evidence supported a triplet code, but this was simply for illustration. Exactly the same results would be obtained if the code operated with groups of, say, 5 bases. Moreover, our symbols + and − must not be taken to mean literally the addition or subtraction of a single base.

It is easy to see that our symbolism is more exactly as follows:

+ represents $+m$, modulo n
− represents $-m$, modulo n

where n (a positive integer) is the coding ratio (that is, the number of bases which code one amino-acid) and m is any integral number of bases, positive or negative.

It can also be seen that our choice of reading direction is arbitrary, and that the same results (to a first approximation) would be obtained in whichever direction the genetic material was read, that is, whether the starting point is on the right or the left of the gene, as conventionally drawn.

Triple Mutants and the Coding Ratio

The somewhat abstract description given above is necessary for generality, but fortunately we have convincing evidence that the coding ratio is in fact 3 or a multiple of 3.

This we have obtained by constructing triple mutants of the form (+ with + with +) or (− with − with −). One must be careful not to make shifts

Table 3. Triple Mutants having a Wild or Pseudo-wild Phenotype

FC (0 + 40 + 38)
FC (0 + 40 + 58)
FC (0 + 40 + 57)
FC (0 + 40 + 54)
FC (0 + 40 + 55)
FC (1 + 21 + 23)

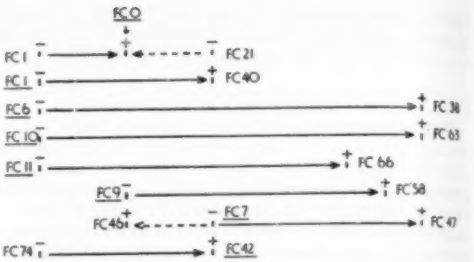

Fig. 4. A simplified version of the genetic map of Fig. 2. Each line corresponds to the suppressor from one mutant, here underlined. The arrows show the range over which suppressors have so far been found, the extreme mutants being named on the map. Arrows to the right are shown solid, arrows to the left dotted

across the 'unacceptable' regions for the ← shifts, but these we can avoid by a proper choice of mutants.

We have so far examined the six cases listed in Table 3 and in all cases the triples are wild or pseudo-wild.

The rather striking nature of this result can be seen by considering one of them, for example, the triple (*FC* 0 with *FC* 40 with *FC* 38). These three mutants are, by themselves, all of like type (+). We can say this not merely from the way in which they were obtained, but because each of them, when combined with our mutant *FC* 9 (—), gives the wild, or pseudo-wild phenotype. However, either singly or together in pairs they have an *r* phenotype, and will not grow on *K*. That is, the function of the gene is absent. Nevertheless, the combination of all three in the same gene partly restores the function and produces a pseudo-wild phage which grows on *K*.

This is exactly what one would expect, in favourable cases, if the coding ratio were 3 or a multiple of 3.

Our ability to find the coding ratio thus depends on the fact that, in at least one of our composite mutants which are 'wild', at least one amino-acid must have been added to or deleted from the polypeptide chain without disturbing the function of the gene-product too greatly.

This is a very fortunate situation. The fact that we can make these changes and can study so large a region probably comes about because this part of the protein is not essential for its function. That this is so has already been suggested by Champe and Benzer[13] in their work on complementation in the r_{II} region. By a special test (combined infection on *K*, followed by plating on *B*) it is possible to examine the function of the *A* cistron and the *B* cistron separately. A particular deletion, 1589 (see Fig. 5) covers the right-hand end of the *A* cistron and part of the left-hand end of the *B* cistron. Although 1589 abolishes the *A* function, they showed that it allows the *B* function to be expressed to a considerable extent. The region of the *B* cistron deleted by 1589 is that into which all our *FC* mutants fall.

Joining two Genes Together

We have used this deletion to re-inforce our idea that the sequence is read in groups from a fixed starting point. Normally, an alteration confined to the *A* cistron (be it a deletion, an acridine mutant, or any other mutant) does not prevent the expression of the *B* cistron. Conversely, no alteration within the *B* cistron prevents the function of the *A* cistron. This implies that there may be a region between the

two cistrons which separates them and allows their functions to be expressed individually.

We argued that the deletion 1589 will have lost this separating region and that therefore the two (partly damaged) cistrons should have been joined together. Experiments show this to be the case, for now an alteration to the left-hand end of the *A* cistron, if combined with deletion 1589, can prevent the *B* function from appearing. This is shown in Fig. 5. Either the mutant *P*43 or *X*142 (both of which revert strongly with acridines) will prevent the *B* function when the two cistrons are joined, although both of these mutants are in the *A* cistron. This is also true of *X*142 *S*1, a suppressor of *X*142 (Fig. 5, case *b*). However, the double mutant (*X*142 with *X*142 *S*1), of the type (+ with −), which by itself is pseudo-wild, still has the *B* function when combined with 1589 (Fig. 5, case *c*). We have also tested in this way the 10 deletions listed by Benzer[7], which fall wholely to the left of 1589. Of these, three (386, 168 and 221) prevent the *B* function (Fig. 5, case *f*), whereas the other seven show it (Fig. 5, case *e*). We surmise that each of these seven has lost a number of bases which is a multiple of 3. There are theoretical reasons for expecting that deletions may not be random in length, but will more often have lost a number of bases equal to an integral multiple of the coding ratio.

It would not surprise us if it were eventually shown that deletion 1589 produces a protein which consists of part of the protein from the *A* cistron and part of that from the *B* cistron, joined together in the same polypeptide chain, and having to some extent the function of the undamaged *B* protein.

Is the Coding Ratio 3 or 6 ?

It remains to show that the coding ratio is probably 3, rather than a multiple of 3. Previous rather rough extimates[10,14] of the coding ratio (which are admittedly very unreliable) might suggest that the coding ratio is not far from 6. This would imply, on our theory, that the alteration in *FC* 0 was not to one base, but to two bases (or, more correctly, to an even number of bases).

We have some additional evidence which suggests that this is unlikely. First, in our set of 126 mutants produced by acridine yellow (referred to earlier) we have four independent mutants which fall at or

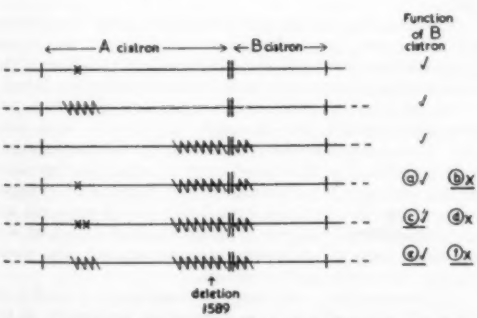

Fig. 5. Summary of the results with deletion 1589. The first two lines show that without 1589 a mutation or a deletion in the *A* cistron does not prevent the *B* cistron from functioning. Deletion 1589 (line 3) also allows the *B* cistron to function. The other cases, in some of which an alteration in the *A* cistron prevents the function of the *B* cistron (when 1589 is also present), are discussed in the text. They have been labelled (*a*), (*b*), etc., for convenience of reference, although cases (*a*) and (*d*) are not discussed in this paper. ✓ implies function; × implies no function

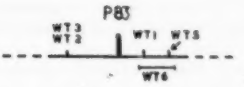

Fig. 6. Genetic map of *P* 83 and its suppressors, *WT* 1, etc. The region falls within segment *B*9*a* near the right-hand end of the *B* cistron. It is not yet known which way round the map is in relation to the other figures

close to the *FC* 9 site. By a suitable choice of partners, we have been able to show that two are + and two are −. Secondly, we have two mutants (*X*146 and *X*225), produced by hydrazine[15], which fall on or near the site *FC* 30. These we have been able to show are both of type −.

Thus unless both acridines and hydrazine usually delete (or add) an even number of bases, this evidence supports a coding ratio of 3. However, as the action of these mutagens is not understood in detail, we cannot be certain that the coding ratio is not 6, although 3 seems more likely.

We have preliminary results which show that other acridine mutants often revert by means of close suppressors, but it is too sketchy to report here. A tentative map of some suppressors of *P* 83, a mutant at the other end of the *B* cistron, in segment *B* 9*a*, is shown in Fig. 6. They occur within a shorter region than the suppressors of *FC* 0, covering a distance of about one-twentieth of the *B* cistron. The double mutant *WT* (2 + 5) has the *r* phenotype, as expected.

Is the Code Degenerate?

If the code is a triplet code, there are 64 (4 × 4 × 4) possible triplets. Our results suggest that it is unlikely that only 20 of these represent the 20 amino-acids and that the remaining 44 are nonsense. If this were the case, the region over which suppressors of the *FC* 0 family occur (perhaps a quarter of the *B* cistron) should be very much smaller than we observe, since a shift of frame should then, by chance, produce a nonsense reading at a much closer distance. This argument depends on the size of the protein which we have assumed the *B* cistron to produce. We do not know this, but the length of the cistron suggests that the protein may contain about 200 amino-acids. Thus the code is probably 'degenerate', that is, in general more than one triplet codes for each amino-acid. It is well known that if this were so, one could also account for the major dilemma of the coding problem, namely, that while the base composition of the DNA can be very different in different micro-organisms, the amino-acid composition of their proteins only changes by a moderate amount[16]. However, exactly how many triplets code amino-acids and how many have other functions we are unable to say.

Future Developments

Our theory leads to one very clear prediction. Suppose one could examine the amino-acid sequence of the 'pseudo-wild' protein produced by one of our double mutants of the (+ with −) type. Conventional theory suggests that since the gene is only altered in two places, only two amino-acids would be changed. Our theory, on the other hand, predicts that a string of amino-acids would be altered, covering the region of the polypeptide chain corresponding to the region on the gene between the two mutants. A good protein on which to test this hypothesis is

the lysozyme of the phage, at present being studied chemically by Dreyer[17] and genetically by Streisinger[16].

At the recent Biochemical Congress at Moscow, the audience of Symposium I was startled by the announcement of Nirenberg that he and Matthaei[18] had produced polyphenylalanine (that is, a polypeptide all the residues of which are phenylalanine) by adding polyuridylic acid (that is, an RNA the bases of which are all uracil) to a cell-free system which can synthesize protein. This implies that a sequence of uracils codes for phenylalanine, and our work suggests that it is probably a triplet of uracils.

It is possible by various devices, either chemical or enzymatic, to synthesize polyribonucleotides with defined or partly defined sequences. If these, too, will produce specific polypeptides, the coding problem is wide open for experimental attack, and in fact many laboratories, including our own, are already working on the problem. If the coding ratio is indeed 3, as our results suggest, and if the code is the same throughout Nature, then the genetic code may well be solved within a year.

We thank Dr. Alice Orgel for certain mutants and for the use of data from her thesis, Dr. Leslie Orgel for many useful discussions, and Dr. Seymour Benzer for supplying us with certain deletions. We are particularly grateful to Prof. C. F. A. Pantin for allowing us to use a room in the Zoological Museum, Cambridge, in which the bulk of this work was done.

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SCIENCE AND WORLD AFFAIRS

THE Seventh Pugwash Conference on Science and World Affairs was held at Stowe, Vermont, during September 5–9. Forty-one scientists from twelve countries attended the Conference*.

This Conference had as its theme "International Co-operation in Pure and Applied Science". The previous conferences have been chiefly concerned with ways of preventing the misuse of science in the wholesale destruction of mankind. In this Conference at Stowe, constructive international co-operation in science was discussed, because it is a way to create trust between nations, a trust which develops from common interests and from experience in working together.

Science misused by nations to foster their competitive interests as world powers makes possible the destruction of mankind. Science used co-operatively by all nations for the increase of human knowledge and the improvement of man's productive capacity can give all men on Earth a satisfactory and worthwhile life. Scientists bear a responsibility both to foster the constructive use of science and to help in preventing its destructive use.

The deliberations of the Conference were carried out in plenary sessions and in meetings of working groups. Similar suggestions for co-operative research activities arose independently from different working groups, and this is reflected in several places in the statement. This is a welcome indication of the essential unity in science. The discussions were carried on in a spirit of friendly co-operation, and full agreement was reached by the entire Conference on the suggestions enumerated here.

* Sir John Crawford (Australia); Prof. Hans Thirring (Austria); Prof. C. Pavan (Brazil); Prof. G. Nadjakov (Bulgaria); Prof. G. Burkhardt (Federal Republic of Germany); Sir Edward Bullard, Prof. A. Haddow, Sir Ben Lockspeiser, Prof. J. Rotblat (Great Britain); Prof. F. B. Straub (Hungary); Dr. G. Bernardini (Italy); Prof. T. Toyoda (Japan); Prof. B. V. A. Röling (Netherlands); Academician A. A. Blagonravov, Academician N. N. Bogolubov, Academician M. M. Dubinin, Prof. V. M. Khvostov, Academician N. M. Sisakian, Prof. N. A. Talensky, Academician I. E. Tamm, Academician A. V. Topchiev (U.S.S.R.); Prof. Harrison Brown, Dr. William Consolazio, Prof. Paul Doty, Prof. Bentley Glass, Prof. C. O'D. Iselin, Dr. Martin Kaplan, Prof. Chauncey Leake, Prof. Linus Pauling, Prof. Jay Orear, Prof. W. Pickering, Mr. Gerard Piel, Prof. I. Rabi, Prof. Eugene Rabinowitch, Dr. Roger Revelle, Prof. Alexander Rich, Prof. Walter Rosenblith, Dr. Eugene Staley, Dr. Alvin Weinberg, Prof. Eugene Wigner, Prof. J. R. Zacharias (United States).

(I) Co-operation in the Earth Sciences

The planet Earth is the common abode of all humans. They have a common interest, both intellectual and practical, in increasing the knowledge of the structure and dynamics of the Earth.

The following proposals were made by the Conference.

(*A*) *A survey of the entire ocean in three dimensions.* (1) *The ocean floor.* An international programme was proposed to develop a detailed map of the floor of the world ocean, including sub-bottom reflecting layers.

(2) *Waters of the ocean.* An international programme should be devised to survey and map the three-dimensional distribution of temperatures, salinity, density, dissolved oxygen, and nutrient salts, under average conditions, of the ocean and synoptic surveys to develop the broad picture of seasonal and shorter-period changes in more limited areas, as well as the study of the interactions among the major bodies of water in the ocean.

(3) *Ocean life.* An international survey and mapping showing the major biological provinces of the ocean and determination of the fertility of the waters at all levels in the food chain and the standing crop of food materials available for human use should be undertaken.

(*B*) *Earth's crust and mantle. Deep drilling programme.* The objective of drilling through the

Earth's crust to the mantle at selected points around the globe presents many unsolved technical problems which call for international collaboration. It was agreed, therefore, that the calling of an international conference on these problems is an urgent first step.

(*C*) *Total environmental forecasting.* An international conference should be called to consider and to organize the establishment of a world-wide network of radio-telemetering observational buoys. This system of buoys would render continuous reports on atmospheric conditions and so contribute to the completion of the world weather map. It would also continuously monitor the energy and water vapour energy exchange between the ocean and the atmosphere, and would observe the changes in the flow of ocean currents in three dimensions. Over a sufficiently long time-period, such a network of buoys would help to assign reliable values to the rate of overturn of the ocean as a whole, a key problem in both climatological forecasts and in the safe disposal of radioactive wastes at sea. The hydrographic offices of the major maritime nations, as well as the World Meteorological Organization, should be encouraged to stimulate such a programme.

(*D*) *Resources.* (1) *Fresh water.* The rising world population and the increasing concentration of that population in metropolitan centres is already pressing on the water resources easily available for direct human consumption, for industrial purposes, and for agriculture. It was agreed that an international conference should be called to consider the organization of an international hydrological decade for the study of the many unknowns that surround this ominous development.

(2) *Living resources of the ocean.* Acre per acre the oceans to-day sustain at least as large a plant crop on the average as does the land, yet man now gets only about 1 per cent of his food requirements from the sea. The oceans, therefore, offer a means for the rapid solution of the protein deficiency afflicting two-thirds of the world population. It is apparent that these resources can best be exploited to this end through international co-operation. The ultimate aim should be to elevate the fishing industry from a hunting industry to an agricultural technology.

(3) *Mineral resources of the ocean floor.* Recent investigations of the ocean floor show a vast reserve of minerals, especially nickel, cobalt, copper and manganese. By means of bottom-photography organized on a world-wide basis, the potentiality of this reserve may be more fully assessed. The necessary observational programme could be organized by the Scientific Commission for Oceanographic Research.

(4) *Natural catastrophes.* Earthquakes, tsunamis, volcanic eruptions, hurricanes and tornadoes constitute the principal hazards of this kind.

With respect to the first three, a better international seismological network, including better instrumentation and distribution of stations, is required. More detailed studies of hurricanes and tornadoes would reveal whether or not man can exert some control over these phenomena.

To implement these programmes, it is recommended that in so far as possible existing international organizations be the means of furthering these programmes.

(II) Co-operation in Space Research

Though the Conference felt that there should be close co-operation in space research it should be realized that complete co-operation in this field, as in some others, will become possible only when the arms race is ended, international tensions are reduced, complete and general disarmament becomes a reality, and the need for secrecy disappears. But certain advances in the presently established co-operation in space are possible now, and certain others could be studied now with the hope of realization in the not too distant future.

(*A*) First, an increase in the exchange of scientific information in areas such as the physics of space and the effects of the space environment on life is recommended. It is further recommended that periodic international symposia be devoted to such subjects.

(*B*) The exchange of methods, and of information on instruments, for scientific space studies which have no military importance is also recommended.

(*C*) The orderly assignment and use of radio frequencies in space should be encouraged. Strong support should be given to the initiative in this direction taken by the International Telecommunications Union, and it is to be hoped that a final solution can be reached within two years.

(*D*) The expansion of existing systems of satellite tracking stations is recommended. Bilateral agreements between different nations, including (within the limits of military security) an agreement between the United States and the U.S.S.R., on the common use of tracking stations; such a bilateral agreement could serve as the first step in this direction.

(*E*) International agreement should be reached on a co-ordinated programme for the use of rocket and satellite during the Quiet Sun Year (planned for the second half of 1962).

(*F*) Similar agreement should be reached on co-operation in the use of rockets and satellites in the projected world magnetic survey. This agreement should include arrangements for simultaneous observation from satellites launched into different orbits by different nations. This co-operation could be organized in the framework of the Committee on Space Research.

(*G*) The desirability of international world-wide systems of communications satellites and of meteorological satellites is endorsed by the Conference, since these would clearly be in the interests of all mankind. It is realized that certain difficulties now stand in the way, but it is to be hoped that the Governments of the United States and the U.S.S.R., as well as of other nations embarking on rocket and satellite programmes, will undertake a common study of the ways to overcome them.

(*H*) It is recommended that co-operation should be established in the instrumental study of the Moon, and also that the basic principles of the International Antarctic Treaty be applied to the Moon and other cosmic bodies.

(*I*) The calling of an international conference or symposium to consider how to avoid the biological and radioactive contamination of extra-terrestrial bodies is strongly urged.

(III) Co-operation in the Life Sciences

Among the many fields of biology in which international co-operation is possible, some are particularly well suited by their nature and importance for combined efforts. These, which relate especially to the promotion of human welfare, have been given primary concern by the Conference.

(*A*) *Biological aspects of food resources.* One of the most important problems facing humanity is that of assuring an adequate supply of food. Adequate biological information now exists to enhance considerably food production in low-yield areas. This can be done most effectively by the development of regional agricultural experiment stations, which can deal with the problem of developing agricultural methods suitable to the local terrain, as well as the long-term problem of breeding plants and animals which are able to thrive in the specific locality. These local agricultural experiment stations should be co-ordinated with an international centre.

It is recommended that existing marine biological laboratories be united into an international system, perhaps under the International Union of Biological Sciences, to ensure permanent support and increase in number.

(*B*) *Preservation and promotion of health.* The health sciences offer one of the most rewarding meeting grounds for international co-operation in science. Increased international co-operation and financial support are essential for the realization of important advances in such fields as cancer, cardiovascular disease, immunology, infectious diseases, mental health, environmental sanitation, problems of ageing, nutrition, human genetics, and others.

International institutes of health devoted to these problems should be established in one carefully chosen place to serve as a world centre of medical research. Smaller subsidiary institutes oriented towards more specialized problems or regional needs (space medicine, medical entomology, tropical medicine) should be established in different countries.

(*C*) *The environment and its modification by man.* The exponential growth of human populations and the accompanying industrial, agricultural and scientific activities have given rise to a number of serious problems, including pollution of air and water resources, which are of considerable biological importance. Especially grave are the problems involving contamination of air, soil and water with radioactive substances. Included here, as well as the more obvious problem of fall-out from nuclear explosions, there is the matter of the safe disposal of radioactive wastes. More international attention should also be directed toward the problems of chemical pollution of air and water. International conferences on these topics should be encouraged.

The extinction of many plant and animal species seems possible. There are large forest and game reserves in the newly formed African countries which are seriously threatened to-day because of a shortage of funds and trained personnel. This problem has been considered by a committee on ecology in the International Council of Scientific Unions. A system of world-wide institutes should be established for preserving indigenous strains of plants, animals and micro-organisms.

(*D*) '*Endless frontiers*'. There has been a great development recently in our understanding of the structure and function of biological macromolecules and the central role of the nucleic acids and the mechanism which relates the nucleic acids to the protein molecules. These developments have a significant bearing on the problems of cancer as well as the broader fields of molecular evolution and the origin of life. Intense interest in this field has developed among scientists in all countries, and it may be possible to capitalize on this enthusiasm by developing an intercontinental institute of molecular biology.

Both the United States and the U.S.S.R. have announced that they are planning to carry out manned exploration of space. It is not unreasonable to suggest that some of the biological developmental work be carried out in common. A considerable saving of time and money would ensue from joint research projects in this area. In addition, some of the instruments which man uses in space for his scientific investigations could be included in this co-operative programme. Joint precautions must be exerted to prevent the contamination of extra-terrestrial bodies by terrestrial organisms.

At the present time an International Biological Programme is under discussion by the International Council of Scientific Unions. Many of the projects described above may be included in the Programme, which if carried out broadly and effectively, would have considerable scientific value as well as a favourable impact on public opinion.

(IV) Co-operation in the Physical Sciences

Modern physical science has in many of its aspects become very big and expensive. It therefore lends itself particularly well to intercontinental co-operation in which the costs are shared and the results are made available to all mankind.

Four specific areas of physical science were identified as being ripe for vigorous action on an intercontinental basis. These areas are the following:

(*A*) *High-energy physics.* Co-operation could centre around the establishment of a laboratory the main research tool of which would be an accelerator of not less than 300×10^9 eV. and of a design which would achieve success in the shortest possible time.

(*B*) *Controlled thermonuclear and plasma research.* In the field of controlled thermonuclear research there has been much effective exchange of information and scientists. This development is particularly significant since this research, prior to 1955, was secret. It is urged that such collaboration be broadened; in particular, that the world's thermonuclear laboratories remain open to scientists of all nations who can contribute to this interesting and potentially important field of research.

Although a new, very large thermonuclear device is probably not needed immediately, still there is a large field of general research in plasma physics which could well be advanced by the establishment of an intercontinental laboratory.

(*C*) *Ultra-heavy element chemistry.* Two different devices are needed for such investigations: high-flux reactors, and heavy-ion, high-current cyclotrons.

It is recommended that an intercontinental centre devoted to investigation of the properties of the ultra-heavy elements be established. The centre probably should be equipped with the most powerful available heavy-ion cyclotron and with equipment for handling the materials. The ultra high-flux reactor (10^{16} neutrons/cm.^{2}/sec.), because of its hazard, probably should be located at a different, more isolated site.

(*D*) *Large-scale computers.* The development of the large modern electronic computer with its enormous memory and high speeds represents one of the most significant scientific events of the past two decades. The future development of these computing machines, with larger memories and higher speeds by orders of magnitudes, would be of immense value to science. Such computing machines will cost perhaps as much as 100×10^6 dollars.

The development of such computers would be a suitable project for international co-operation. The utilization of such a machine will advance not only mathematics but also all the physical sciences and the biological sciences, particularly the unravelling of the structure of macromolecules. It would also find great utility in economics and other social sciences.

(*E*) *A globular cluster of big science centres.* It is believed that the separate big science laboratories in high-energy physics, heavy-element chemistry, macromolecular biology, health research, and possibly thermonuclear research, will prosper better if they are reasonably close together than if they are completely isolated from each other. The intercontinental computing centre will be more viable and will be a better centre if it were the nucleus of such a cluster.

The Conference urged that the intercontinental scientific laboratories be located in relative geographical proximity and that they be served by the intercontinental computing centre. Such a centre, comprising much of what is called 'big science', would represent a capital investment of about 5×10^9 dollars. It is believed that the astute location of such a striking epitome of science—the most characteristic theme of our modern civilization—could have extraordinarily great significance in improving the tone of the present political situation.

(V) Co-operation in Assistance to Developing Nations

Assistance to developing countries is a duty and necessity for all countries. This aid should be rendered so that it would not impair the independence of any country.

Greater support for international co-operation in assistance to developing nations is needed. Such co-operation could help to reduce world tensions, to strengthen peace, and to further disarmament. Disarmament would in turn improve the climate for international co-operation in this and other fields and make available additional funds which could and would be used to increase the assistance to developing nations. Clearly, the greatest co-operation and the release of maximum funds for the assistance programme could be achieved by complete disarmament.

Scientists have a definite part to play in the development of assistance programmes and special emphasis should be placed on this subject in subsequent conferences. Such a conference should include a large participation of representatives from the developing nations.

The recommendation from the Economic and Social Council that a conference on science and technology in application to the problems of new nations should be held next summer in Geneva under United Nations sponsorship is to be welcomed.

A subject of interest to scientists is that of natural resources of different areas and of their population trends. Unprejudiced quantitative study of the latter topic should be carried out on an international, co-operative basis. Another topic for similar co-operative research is world nutrition, including the study of reasons for widespread occurrence of avoidable malnutrition in many parts of the world. The problems of energy supply, particularly in areas in which the demand for energy is diffused rather than concentrated in large industrial centres, calls for a similar study. It is suggested that preliminary study groups on these problems be organized prior to the above-mentioned conference.

An international study should also be made of the advisability and practicability of establishing an international fund to which individual scientists from countries in which local funds are insufficient for this purpose could apply for assistance in their scientific research.

(VI) Exchange of Scientists and Scientific Information

By its very nature and tradition science is a universal enterprise. The rapid exchange of information, mutual visits of scientists and their working as guests in the laboratories of other scientists constitute the main pathways of scientific collaboration among scientists all over the world. It is to be noted that there has been substantial progress in recent years in the area of scientific exchange. Yet it is to be regretted that there exists a number of difficulties which interfere in major ways with the further broadening of scientific collaboration and exchange.

(*A*) *Exchange of scientists.* The planned exchange of scientific personnel initiated by the Bronk–Nesmeyanov and similar agreements should be considerably increased. The visits should be extended over periods sufficient for the completion of research projects. In addition to planned exchange, the framework of these agreements should allow for and encourage invitations to scientists in the country in which they are to visit, and for the invited scientists to be able to accept such invitations. Application of the *quid pro quo* principle to visits under the agreement (that is, the exchange of one solid-state physicist for another solid-state physicist, etc.) has tended to hamper fruitful exchange, and it is urged that such regulations be set aside in future agreements.

The role of Government bureaucracies in the administration of these agreements should be minimized. To implement this recommendation, governments should be urged to expedite visas and passports for scientists, since past and present failures in this respect have seriously hampered scientific exchange. The scientific organizations of various nations should consider ways to facilitate the travel of pre- and post-doctoral fellows across national boundaries to study for adequate periods of time (one year or more) at research centres and under teachers where their training and scientific maturation can be best enhanced.

(*B*) *Exchange of information.* Noting the obstacle to the exchange of scientific information presented by the mounting volume of current publication, which is increasing exponentially and doubling about every decade, the situation calls for radical measures of rationalization. Among potentially useful measures are the following: to review and co-ordinate the character and content of journals published in all countries with the view of reducing the number of journals which a scientist must follow to keep abreast of work in his discipline; to institute standard formats for the presentation of scientific papers; to formulate a standard system for the annotation of the contents of published papers suitable for coding and manipulation by machines for the storage and retrieval of information; to institute regional depots under international co-ordination to store complete experimental records and other documentation in support of the brief published papers; to make such material rapidly available to interested scientists; to

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consolidate the abstracting services now carried on independently in many countries, a measure that could reduce present duplication of effort by a conservatively estimated factor of three.

The publication of international review journals of two types as follows is recommended: interdisciplinary review journals written in relatively non-technical language for the benefit of scientists in different disciplines, and more specialized review journals which would keep scientists working in a given area abreast of the work going on in the same or related areas all over the world.

All Governments are recommended to open their postal systems to the untrammelled flow of scientific publications whatever their country of origin or destination.

LAND USE IN ARID REGIONS

THE arid zone programme of the United Nations Educational, Scientific and Cultural Organization, one of the Organization's three major projects, has yielded several valuable reviews of research and proceedings of symposia, mostly devoted to hydrology and ecology. The latest in the series, a volume of some 350,000 words reviewing the history of land use in arid regions, is of more general interest*. It deals with all the main dry lands with two main exceptions, those surrounding Abyssinia and those of South America in post-Columbian times.

F. K. Hare explains the widespread aridity in subtropical latitudes in terms of the divergent wind-flow at low levels related to high pressure at 2–3 km., and considers it unlikely that any past climatic epoch can have been free of tropical aridity. He finds it inconceivable that man can significantly alter the régime, the energy transformations involved are on so large a scale. Thus the flooding of desert depressions, for example, would have only very modest effects on neighbouring areas.

A summary by K. W. Butzer of what is known about climatic change in arid lands since the Pliocene sets the regional histories in a longer time perspective. Full aridity was achieved in most arid lands some 15,000 years ago. Since then there has been no progressive desiccation, only minor fluctuations of climate. Of especial interest are those fluctuations which might possibly have affected the environment of man when he was first beginning to manage crops and animals in south-west Asia ten thousand years ago and in Mexico possibly not much later.

Changes in climate over the past two or three thousand years are scarcely detectable with certainty until the fluctuation of the past three centuries. This has involved more than the spectacular rapid advance and current retreat of Alpine glaciers, for it is becoming clear that semi-arid lands in many parts of the world have been receiving less rain in recent decades than in the latter half of the nineteenth century. The dry trend continues, and the further outlook is unsettled.

Prof. Dudley Stamp, the editor of the volume, points out that a knowledge of the climate is not enough to allow a reconstruction of the past vegetation cover. The effects of burning and of a more prolific fauna have also to be taken into account. Ecologists and archæologists working together in the field are beginning to produce fairly reliable pictures of ancient landscapes, and R. O. Whyte, in his contribution on south-east Asia, sees much promise in this type of co-operative research.

South-west Asia is in many ways the most important of the regions and at the same time it produces the greatest difficulties in comprehension because of the mass of information available from widely scattered sites and conflicting interpretations of evidence. Whyte's review is very stimulating but not at all easy to digest. Egypt is of its nature simpler, and the material presented by G. Hamdan will be more familiar to many readers. V. A. Kovda's survey of the Russian plains, the Caucasus and Central Asia (plus a few pages on irrigation in China) naturally lays great stress on the revolutionary effects of introducing socialist methods of production to the steppe. The scale of operations is indeed impressive. Kovda notes the steady increase in the frequency of *sukhovei*, dry dusty winds, but asserts that their effects will be mitigated by new forests and irrigation projects which, he says, are expected to increase precipitation.

J. Despois, writing on North Africa, agrees with Butzer that there is no good evidence that the climate there was much more favourable to farming in the Roman period than in later times. The decline in agriculture can mainly be attributed to eleventh-century and later invasions of Bedouin Arabs from the east. Even their destructiveness seems to have been far exceeded by those other nomadic herdsmen, the Mongols, who descended on western Asia two centuries later. From both, recovery was slow, and in Cyrenaica and parts of Iraq and Iran is still incomplete.

Nomadism is a rational response to those seasonal and year-to-year variations in grazing and surface water typical of arid regions. R. F. Logan describes flocks in the United States being driven in double-decker trucks to summer grazing in upland meadows under Forest Service permits. Everywhere some State control of nomadism seems to be inevitable. Although, as Th. Monod and Ch. Toupet note in the Saharan region, an irreversible process of "sedenterization" has set in since pacification, progress in this direction is likely to be too slow to satisfy administrators and conservationists.

Innovations bring old problems. Perennial irrigation can lead to salt accumulation and waterlogging, as in the Punjab, and to bilharzia and other diseases. Improved water supplies from deep wells can accentuate overgrazing. The balance is delicate in arid lands and the regulating mechanism must work efficiently or disaster comes swiftly. This seems to be the main lesson to be learned from the past.

For the future, the possibilities of industry based on local minerals, with space-cooling and a sunny climate to attract labour, are becoming apparent from recent developments in Arizona and Central Asia. The process of urbanization is not new to the arid lands, it probably began there, and may well go further there than anywhere else in the world.

A. T. GROVE

*United Nations Educational, Scientific and Cultural Organization. Arid Zone Research No. 17: *A History of Land Use in Arid Regions*. Edited by L. Dudley Stamp. Pp. 368. (Paris: Unesco; London: H.M.S.O., 1961.) 37 N.F.; 52*s.* 6*d.*; 10.50 dollars.

OBITUARIES

Dr. B. L. Goodlet, O.B.E.

THE death occurred on October 27 of Dr. Brian Laidlaw Goodlet, deputy chairman of the Brush Electrical Engineering Co., and, until recently, its managing director.

Brian Goodlet was born in St. Petersburg in 1903 of British parents who had settled in Russia in the service of the Government, and was educated at the Imperial School in St. Petersburg. He escaped from Russia during the Revolution and received his further training with Vickers, Ltd., and Metropolitan-Vickers, first at the Attercliffe Works, Sheffield, studying in the Applied Science Department of the University of Sheffield, where he gained the associateship in electrical engineering, and then as a special trainee in the Trafford Park Works. In 1924 he was appointed to the staff in charge of the first High-voltage Laboratory, and there he introduced to the Company high-frequency and impulse voltage testing of electrical products, and made important contributions to the study of transmission and bushing insulators, during which time he designed the second High-voltage Laboratory equipped for a million volts. He also designed the very small high-voltage generator which the Metropolitan-Vickers Co. gave to the Cavendish Laboratory to assist me in the first attempts to accelerate particles to very high energy for transmutation experiments, and then designed the special high-voltage transformer of extremely small dimensions which was used by Cockcroft and Walton in their 1932 experiments. There were no other high-voltage transformers in those days which could have fitted into the small rooms of the Cavendish Laboratory, and we owe Goodlet a great debt for these expert designs: without them Britain might not have been ahead of the large American laboratories.

It was through his contacts with the Cavendish Laboratory that he decided to take the Engineering Tripos in Cambridge, leaving Manchester at the age of twenty-seven with a generous grant from the Company. On his return to Trafford Park he made a detailed study of extra high-voltage turbo-alternators, and also wrote his classic paper on lightning.

In 1937 Goodlet was appointed to the chair of electrical engineering in Cape Town, but he returned to Britain in 1939 to take up the chair in Birmingham. He offered his services to the Admiralty, but, because of his former connexion with Russia, he was not accepted; so he applied to return to the still vacant chair in South Africa, where he immediately joined the South African naval work on the degaussing of ships in Cape Town Harbour, ultimately gaining the rank of commander in the South African Navy. After a short time he was sent to England to work with the British Admiralty as chief scientist at Rosyth, where he made distinguished contributions to work on underwater explosions, before joining the Far East Naval Task Force in Ceylon under Lord Mountbatten. He was made O.B.E. for his war services. In 1946 he returned to Cape Town, where he built up a vigorous electrical engineering department with almost pitiable funds, gathering around him several engineers from the Metropolitan-Vickers Co. and starting a lively research school; but this had scarcely begun to bear fruit when he returned to England again in 1950, this time as deputy chief engineer of the Atomic Energy Establishment at Harwell. His text-book on basic electrotechnics—the result of his post-war work in South Africa—has become well established in British universities for second- and third-year honours engineering students.

Goodlet began in Harwell with a small team, including Mr. R. V. Moore, to investigate in detail the feasibility of a power-producing nuclear reactor system, referred to as *Pippa*, using natural uranium. The team selected graphite as moderator, carbon dioxide as coolant gas and a vertical arrangement of fuel rods, and by 1952 all the main features of the design had been established: it was then handed over to the Production Division to produce Calder Hall. It is a tribute to Goodlet's engineering judgment that no major changes of design were necessary. (His paper, "Nuclear Reactors for Power Generation", to the Institution of Mechanical Engineers, was awarded the Thomas Hawksley Gold Medal.)

During 1952–56 he was the chairman of the Naval Education Advisory Committee of the Admiralty: the Director of the Naval Education Service advises me that he made an ideal chairman and was greatly respected by his colleagues. During Goodlet's period of office, the Committee advised on a number of important matters, including cadet entry into the Royal Navy, officer training, the technical training of junior ratings, the conditions of service of civilian teaching staff at the Royal Naval Colleges, the rehabilitation of the Dockyard Technical Colleges and the organization of facilities for informing the Service of modern developments in science and technology. His untiring interest and wise counsel in all aspects of naval education were of the utmost value to the Director of the Naval Education Service.

By 1956, Goodlet felt that his work at the Atomic Energy Research Establishment was finished, and he joined the Brush Electrical Co., Loughborough, as chief engineer and director, later becoming its managing director. Mr. G. B. R. Feilden tells me that Goodlet was confronted by a series of major breakdowns of 30-MW. double-rotation turbines which had been designed before Goodlet joined the Company. The breakdowns were caused by vibration, and the solution to the problem required the evolution of entirely new measuring techniques: Goodlet was responsible for solving this problem, which was fortunately achieved successfully, largely due to his own perseverance, shortly before his death. He submitted his published work to Cambridge and was awarded the Sc.D. in 1958.

Perseverance and thoroughness characterized all his work: like the great American engineer, Charles Proteus Steinmetz, he was never satisfied until he understood the fundamentals of any problem which confronted him, and he was fondly nicknamed 'Prot' by his closest friends because of this similarity. He invariably wrote out the basic facts and deduced the solution in beautiful handwriting, and his notebooks were a joy to peruse. His perseverance was equally manifest in his hobbies, and he enjoyed going up Table Mountain the hardest way. He was extremely interested in military strategy and it was fascinating to hear him quote Napoleon's campaigns; he even wrote a mathematical paper on the ballistics of

weapons used in classical times. I was present when Rutherford, returning from the British Association meeting in South Africa, recited the exploits of Cetywayo; Goodlet, to Rutherford's great delight, continued the story with intimate details of the part played by the Zulu's lieutenants.

Goodlet is survived by a widow, two sons, and two daughters.

T. E. Allibone

Dr. A. K. Das

India lost a meteorologist of note and a leading astronomer of this century with the death on February 18, 1961, of Anil Kumar Das. He was best known for his work at Kodaikanal Astrophysical Observatory, of which he was the head for fourteen years. At the time of his death, however, he was acting temporarily as director of the Nazamiah Observatory, Hyderabad, and as professor of astronomy at Osmania University. But although best known for his astrophysical researches, Dr. Das published a number of papers on purely meteorological topics, mainly during the early part of his thirty-years service in the India Meteorological Department.

After completing his education to postgraduate level in India, Das continued his studies in Paris under Fabry and later also worked with Max Born and Augenheister. He returned to India in 1930 to commence his meteorological work, but in 1934 he went to England to study the temperature of the Sun by spectro-photographic means at the Solar Physics Observatory, Cambridge. This virtually marks the beginning of his career in astronomy. His many papers on solar physics thereafter appeared at regular intervals almost up to the date of his death.

Das had the intuitive foresight, great energy and determination of the great research worker, but he was also an administrator of considerable ability. Indeed, his greatest achievements probably lie in the improvements he introduced at Kodaikanal, by the installation of new equipment and the initiation of new fields of research. Largely thanks to Das, this Observatory is now carrying out researches and making observations, using the finest equipment, in many branches of geophysics and solar physics. It is a pity that he could not live long enough to fulfil his last ambition to work with his new instruments during the last years of his life.

NEWS and VIEWS

Botany in University College, Dublin : Prof. J. Doyle

Prof. Joseph Doyle has retired from the chair of botany in University College, Dublin, after nearly fifty years service. He entered the College on a mathematical scholarship; later he became interested in biology through the pathway of medicine. Following a period of postgraduate research, part of which was spent in Germany, he was appointed assistant in biology in 1913; at this time, he and two others comprised the staff of the Biology Department. In 1924 he was appointed professor of botany, and undertook the development of the first Department of Botany in the College. His main research interest is represented by a long series of papers on conifer embryology, on which subject he is internationally recognized as an authority. He was awarded the Boyle Medal of the Royal Dublin Society in recognition of this work. The degree of D.Sc. was conferred on him in 1930. At the Dublin meeting of the British Association for the Advancement of Science in 1957, he was president of Section K (Botany). In addition to developing the Department of Botany, Prof. Doyle rendered distinguished administrative service to his College. As dean of the Faculty of Science he showed considerable organizing power; for many years he was a member of the Governing Body of the College and of its Finance Committee. He has helped greatly in furthering the scientific and cultural life of Dublin. He is a member of the Council of the Royal Dublin Society, secretary of the Royal Irish Academy, chairman of the Praegar Committee for Field Natural History, and a trustee of the National Library of Ireland. Recently he has been actively engaged in planning new Science Buildings for University College, Dublin. His many interests will ensure for him rewarding occupation in his retirement.

Prof. Phyllis M. Clinch

Dr. Phyllis M. Clinch has been appointed to succeed Prof. J. Doyle. Dr. Clinch, in fact, majored in chemistry in University College, Dublin, with first-class honours and first place at her primary degree, but, botany being her second subject, she took an immediate interest in plant biochemistry and her earlier research was done in the Department of Botany on problems of seasonal metabolic changes in conifers. In this and in all her subsequent work her early intensive training in basic chemistry proved a most valuable asset. After a period of study under Prof. V. H. Blackman in the Imperial College and Prof. Guilliermond in Paris, she was appointed senior research assistant in plant virus diseases in the Department of Plant Pathology, University College, Dublin. Here she played a major part in the team that produced so much important work on plant viruses, especially the analyses of viruses affecting the potato plant. The value of the work from this Irish School is too well known to need comment here; suffice it to say that Dr. Clinch's share in it has gained her a well-merited international reputation in the plant virus world. In 1950 she accepted an invitation to join the staff of the Botany Department, University College, as senior lecturer with the primary purpose of developing courses and research in plant biochemistry and physiology along modern lines. The very successful organization of this entailed, unfortunately, a temporary break in her work on viruses. The break, however, was only temporary, and in recent years she has initiated a programme of research into the biochemical and physiological effects of virus infection on the metabolism of the infected plants themselves. It is to be hoped that the administrative and other duties which will now naturally fall on her as head of a department will not unduly hamper progress in this promising line of research.

Control of Government Expenditure on Research and Development

In opening a debate on November 30 when the House of Commons was asked to take note of the First, Second and Third Reports from the Committee of Public Accounts in the Session 1960–61 and of the Special Report from that Committee, Mr. H. Wilson referred to the centenary of the establishment of the Committee in April 1861 and to the steady development of its work. The debate covered a fairly wide field, but the two chief points of scientific interest are to be found in the reply of the Financial Secretary to the Treasury, Sir Edward Boyle. Sir Edward, referring to research and development practice, endorsed the Treasury Minute that it is Government practice to rely largely on private industry when it is a matter of design studies for complicated new weapons and equipment, subject to the checks which Government establishments can operate, and that research, development and production are integral parts of a continuous process to which the Ministry of Aviation's research establishments contribute by virtue of their specialized knowledge and facilities. Sir Edward also said that the major part of the Atomic Energy Authority's net cost of operations—nearly £60 million in 1959–60—represents research and development effort in both the civil and military fields, and to publish the civil figures alone would make it easy to estimate the level of military research. Decisions on all matters concerned with the disclosure of information are taken after regular periodical reviews, and the importance of this issue to the Public Accounts Committee was realized. In principle, the Authority hoped to recover its research and development expenditure on civil reactor systems.

Medical Men in Britain

In a debate in the House of Lords on November 29 on the shortage of medical men, Lord Taylor stressed the difficulty which non-teaching hospitals in Britain are experiencing in filling appointments. In replying for the Government, Lord Newton said that after reviewing the data and calculations of the Willink report, the Government is satisfied that the prospective demand for medical services will justify a rise in the university intake of pre-clinical students from Great Britain of 10 per cent above the 1,760 recommended by the Willink Committee. The intake in July 1961 was 1,788. The University Grants Committee has been asked to consider with the universities the implications of the Government's conclusion. Steps are being taken to improve the statistical information so far as reasonably possible. Lord Newton said that the Government intends to watch the figures constantly, including those of output from the medical schools, rather than attempt to make firm estimates at wide intervals of time. Lord Taylor had asserted that the shortage is now showing itself in the teaching hospitals also, and that the hospital service in Britain would have collapsed but for the influx of some 3,000–4,000 junior doctors from India and Pakistan. Lord Newton admitted that in March 1960 more than one-third of the posts in the middle and lower grades were occupied by doctors born outside Britain, but he emphasized the value of these doctors and the debt to their services. He said that in 1960 the average number of patients on a doctor's list was 2,287, about 150 fewer than it was in 1952, and that the improvement of the distribution of doctors was of special concern to the Medical Practices Committee constituted under the National Health Service Act.

Accelerators for Low-energy Nuclear Physics

Recent advances in the theoretical description of the atomic nucleus, together with recent design improvements in cyclotrons and Van de Graaff accelerators, have stimulated a special U.S. National Science Foundation programme for establishing and improving low-energy nuclear physics research facilities. The theoretical advances have resulted in a need for refined measurements of energy-levels, spin assignments, and other characteristics of the nucleus so that the synthesis of present theoretical models can be further advanced. Many of these refined measurements are now possible through extension of the range of Van de Graaff accelerators giving particles with energies of up to 20 MeV., and improvements in cyclotron design to permit well-controlled beams up to 40 MeV. Until about five years ago Van de Graaff accelerators were restricted to energies less than 8 MeV. Recently, the Foundation has made a group of six grants, totalling 4,161,500 dollars, in furtherance of the new programme. These six accelerators are expected to play an important part in the nation's effort in nuclear structure physics. Grants made so far in this special programme are as follows: University of Chicago, 296,700 dollars for a 4-MeV. Van de Graaff machine to be used by Dr. S. K. Allison and his Group; Michigan State University, 700,000 dollars toward a 40-MeV. cyclotron for the use of Dr. Henry G. Blosser's research team; University of Pittsburgh, 977,600 dollars toward an 18-MeV. three-stage Van de Graaff machine for research under the direction of Dr. Bernard L. Cohen; University of Washington (Seattle), 1,240,000 dollars toward a 22-MeV. three-stage Van de Graaff machine for the Physics Department, of which Dr. Ronald Geballe is executive officer; Ohio State University, 499,200 dollars for a 5·5-MeV. Van de Graaff machine for the Department of Dr. H. H. Nielsen; State University of Iowa (Iowa City), 498,000 dollars for a 5·5-MeV. Van de Graaff machine for the Department under Dr. James A. Van Allen.

The Royal Commission for the Exhibition of 1851

The eleventh report of the Commissioners for the Exhibition of 1851 covers the activities of the Royal Commission since its tenth report was issued in May 1951 (Pp. 32. (Cmnd. 1502.) London: H.M.S.O., 1961. 2*s*. 6*d*. net). The general pattern of the Science Research Scholarships has remained unchanged, but the list of universities invited to participate has been extended and the value of the awards increased to £550 a year for Overseas Scholars and £800 a year for senior students, exclusive of allowances. In 1958 the National Research Council of Canada offered to each 1851 Scholar from Canada a bonus of £250 a year from its own funds, which has been particularly useful to married Scholars. Similar arrangements have been made, with various qualifications, by authorities in Australia, South Africa, India, Pakistan and New Zealand. Since 1952 the Commission has co-operated with the Council of the Royal Society in the administration of the Rutherford Scholarship. The value of the Postgraduate Scholarship in Naval Architecture was in 1958 increased to £600 a year. In view of the re-allocation of so much of the property on the Kensington Gore Estate in 1956, it was agreed with the Imperial College of Science and Technology

and Government departments concerned to arrange a new lease to the College for 999 years from midsummer 1956 at a rental commencing at £5,000 and rising over ten years to £25,000 a year.

The Commission's office at 1 Lowther Gardens provides accommodation also for the London headquarters of the British School at Rome, to which the Commission now contributes £8,000 a year, and for the Institute of Physics and the Physical Society. Of the expenditure of £324,759 during the ten years January 1, 1951–December 31, 1960, £244,822 was on direct educational grants. A new *Record of the Science Research Scholars of the Royal Commission for the Exhibition of 1851, 1891–1960*, has now been compiled, and it may be noted that of the 905 Scholars, 99, including 34 from overseas, became Fellows of the Royal Society, of which two were elected president, eight won Nobel Prizes (Pp. iv+107. London: Royal Commission for the Exhibition of 1851, 1961. 12*s*. 6*d*.). The *Record* lists separately Science Research Scholars appointed during 1891–1921, Overseas Scholars appointed since 1922 and Senior Students appointed since 1922. There are indexes to Scholars and to the Institutions from which they came.

Experimental Eye Research

The scientific literature on the eye and vision is dispersed in journals representing many different disciplines, and visual scientists have for long deplored the fact that they had no journal of their own. Now they are to have at least two. For the appearance last June of *Vision Research* (Pergamon Press) (see *Nature*, 191, 650; 1961) is followed by the present debut of *Experimental Eye Research* (Academic Press). Congratulations are due to Academic Press for the fine quality of *Experimental Eye Research*, the first number of which appeared in September (1, No. 1; September 1961. Pp. 97. Published quarterly. Vol. 1, approx. 400 pages. (London: Academic Press, Inc. (London), Ltd.; New York: Academic Press, Inc., 1961). 115*s*.; 16 dollars). The object of this quarterly journal is the publication (in English) of original papers on the anatomy, physiology, biochemistry and biophysics of the eye. "Contributions on such subjects as the production and circulation of ocular fluids, the fine structure, biochemistry, biophysics and metabolism of the eye tissues, the photochemical processes related to visual function, and the neuromuscular mechanisms in the control of eye movements will be preferred." The editors-in-chief are Dr. E. A. Balazs, of Harvard Medical School, and Dr. Hugh Davson, of University College, London. They are supported by a group of leading workers forming an editorial board of five and an advisory board of nine. A study of the first issue reveals a high standard of editorial policy and also confirms the initial impression that the main interests of the publication are the minute anatomy and vegetative physiology of the eye. Since the interests of the 'rival' publication, *Vision Research*, are centred more on the physiology of vision, there is less overlap in the scopes of the two journals than might appear.

Engineering and Television

Two publications of the British Broadcasting Corporation issued to mark the twenty-fifth anniversary of B.B.C. Television direct particular attention to the work done by its engineering division during the period under review. The first, *Twenty-five Years of B.B.C. Television*, is one of its periodic *Monographs*, and has been prepared by one of the original members of the B.B.C., Sir Harold Bishop, now director of engineering (No. 39. Pp. 41 (14 plates). London: British Broadcasting Corporation, 1961. 5*s*.). After a survey of the events and developments which led to the start of the B.B.C.'s high-definition television service, the monograph describes the main engineering developments during the past quarter of a century. Particular attention is directed to those techniques which have been originated by the B.B.C., or which are utilized in a specially noteworthy manner in the services of the B.B.C. There is also a brief review of the B.B.C.'s contributions to probable future developments, including colour television and a change of standards. The second publication, *B.B.C. Television: a British Engineering Achievement*, is written in a more popular style, and gives a narrative account of how television works, the early growth of the services and what engineering services and techniques are involved to bring television into the home. The brochure is well written, with good illustrations and, like so many B.B.C. publications, is remarkably cheap (Second edition, revised. Published on the 25th Anniversary of B.B.C. Television. Pp. 64. London: British Broadcasting Corporation, 1961. 3*s*. 6*d*.). It should find its way to bookstalls as well as libraries in schools and other places.

Astronomical and Nautical Almanacs

Two ephemerides have recently been published for the year 1962, one by the U.S. Government and the other by the Indian Government. *The American Ephemeris and Nautical Almanac* is unchanged with regard to the presentation of material (Pp. vii+514. Washington, D.C.: Government Printing Office, 1960. 4 dollars). *The Indian Ephemeris and Nautical Almanac* (Pp. xxviii+460. Delhi: Manager of Publications, 1961. Rs. 14.00; 22*s*.) is closely similar to the American *Ephemeris*, though more restricted in scope, but in addition contains a section on the Indian Calendar. The 1962 edition contains four new sections: (1) ephemeris for physical observations of the Sun; (2) ephemeris for physical observations of the Moon; (3) centre of mass of the solar system; and (4) local circumstances of occultations of bright stars and planets visible in India.

Technical Publications of the Oak Ridge National Laboratory

The publication *ORNL* 61-6-27 contains a list of papers published in journals and presented at meetings, reports issued, and theses completed, during 1960, by the members of the staff of the Oak Ridge National Laboratory, Oak Ridge, Tennessee (Pp. v+107. Oak Ridge, Tennessee: Oak Ridge National Laboratory, 1961). Reprints of many of the articles can be obtained on request either from the Laboratory, or of papers presented at scientific meetings from the authors concerned. There is an author index, and the various articles are grouped within the sections according to subject, biology, chemistry, physics, etc. The prices of the *ORNL* reports are given, and the reports, except those indicated as 'not for sale', can be obtained through the Office of Technical Services, Department of Commerce, Washington 25, D.C.

National Conference of Standards Laboratories

To help meet the needs of science and industry for improved uniformity and greater precision in calibration and measurements in all areas of the physical

sciences, engineering and technology, a new organization—the National Conference of Standards Laboratories—was established on September 15, 1961, by representatives concerned with standards activities in Government, industry, education, and professional societies of the United States. A major activity of the National Conference will be to arrange a continuing series of standards laboratory conferences. The General Committee, headed by Lloyd B. Wilson, of the Sperry Gyroscope Co., has arranged for the first conference in this series to be held during August 1962 at the National Bureau of Standards Boulder Laboratories, Boulder, Colorado. Another major activity being considered is the establishment of a voluntary system of measurement agreement checks to demonstrate competence and continued uniformity among standards laboratories. Further information can be obtained from Dr. H. W. Lance, Electronics Calibration Center, Boulder Laboratories, National Bureau of Standards, Boulder, Colorado.

Conference on Measurement and Control Technology

THE Society of Instrument Technology and the Royal Dutch Institute of Engineers are organizing a joint conference to be held during April 10–13, 1962, in Amsterdam. The programme is being arranged to encourage discussion and exchange of information on the present state and future trends of measurement and control technology in Britain and Holland. Six technical papers will be presented and discussed covering new measurement methods such as direct reading spectrography, X-ray fluorescence chromatography and optical measuring techniques, descriptions of working automation projects in the biscuit industry and sinking mine shafts, and control in manufacturing industry. While most of the places will be reserved for members of the Society of Instrument Technology, it may be possible to entertain a few applications from non-members. Further information can be obtained from Mr. I. V. Idelson, Mullard Equipment, Ltd., Manor Royal, Crawley, Sussex.

University News :

Birmingham

THE following appointments have recently been announced: Dr. J. S. Brimacombe, to be lecturer in the Department of Chemistry; Dr. D. E. N. Davies, to be lecturer in the Department of Electrical Engineering; Dr. F. Rieband, to be lecturer in the Department of Mechanical Engineering; E. D. R. Shearman, to be senior lecturer in electromagnetism in the Department of Electrical Engineering.

Leeds

IN a statement to a meeting of the Court of the University of Leeds on November 15, when the annual report was presented, the vice-chancellor, Sir Charles Morris, referring to the increase in the number of students by 1,400 in five years, said that in the past year it had increased by 386 to 5,175, and it was probable that this order of increase would continue during the forthcoming quinquennium and that the student population in 1966 would be 6,900. The building programme was based on an increase of this order, but there was some risk that the provision of residential accommodation might seriously fall behind needs in the immediate future. The vice-chancellor also referred at some length to the new courses which the University was offering leading to an honours degree covering study in depth in two of the traditional subjects. These courses were meeting with immediate response, and twenty-one students were expected to graduate this year in the 'combined' courses in arts, the most popular combinations so far being economics and history, English and history, geography and history, and psychology and sociology. The Science Faculty was starting such courses next October and a director of combined studies was being appointed to guide the students following these courses and advise on combinations of subjects. While he did not think the 'special honours' courses would disappear or lose prestige, he thought it would be increasingly accepted that at the standard of first degree at honours-level, two subjects could effectively be studied together in depth.

Sussex

THE following appointments have been made: Dr. D. B. Scott, at present reader in mathematics at King's College, London, to be professor of mathematics; Dr. E. R. A. Peeling, at present senior lecturer in chemistry in the University of Leicester, to be senior lecturer in chemistry.

Announcements

SIR HARRY MELVILLE, secretary of the Department of Scientific and Industrial Research, has been made a member of the Council for Scientific and Industrial Research in recognition of his "notable services to D.S.I.R.". The appointment is personal to Sir Harry and does not mean that future secretaries of the Department of Scientific and Industrial Research will automatically become members of the Research Council.

A SYMPOSIUM on the "Methodology of Plant Eco-Physiology" will be held in the Botanical Institute, 5 rue Auguste Broussonnet, Montpellier, France, during April 7–12, 1962. Further information can be obtained from Dr. F. E. Eckardt, Institut de Botanique, Montpellier, France.

THE Department of Physics and Astronomy of the Ohio State University is organizing a symposium on "Molecular Structure and Spectroscopy", which is to be held in the University during June 11–15. Further information can be obtained from Prof. R. A. Oetjen, Department of Physics and Astronomy, Ohio State University, 174 West 18th Avenue, Columbus 10, Ohio.

DUE to a change in date of the meeting of the International Pharmaceutical Federation, which will be held in Vienna during September 1–24, 1962, the third British Congress on the History of Medicine and Pharmacy will be held in London during September 27–28, 1962. The subject of the Congress will be "The History of British Hospitals". Further information can be obtained from Dr. F. N. L. Poynter, Wellcome Historical Medical Library, Euston Road, London, N.W.1.

ERRATUM: We regret to find that, in the article entitled "Action of Radiation on Synthesis of Deoxyribonucleic Acid in Normal and Tumour Strain Cells" (*Nature*, December 9, p. 944), a line has been omitted and another duplicated. In column 2, p. 944, lines 15 and 16 should read: " . . . a decrease from the consequent depletion of the cell population. However, as Painter and . . . " The present line 16 is a repetition of line 13.

INTERPRETATION OF GEOPHYSICAL SURVEYS

RECENT improvements in geophysical instruments have not simplified interpretation of the data obtained by using them. Indeed, their greater speed and higher accuracy increase the data to be analysed and foster attempts to interpret in finer detail. Assessment of factors controlling the reasonable limits of interpretation was the main aim of a Geophysical Discussion of the Royal Astronomical Society, held in association with, and at the rooms of, the Geological Society on October 27. Introducing the four invited speakers, the chairman, Dr. W. Bullerwell (Geological Survey), remarked that geophysical interpretation is usually tested by subsequent geological exploration; thus it was appropriate that discussion about interpretation should take place among geologists and benefit from their comment.

In opening the discussion, Prof. J. M. Bruckshaw (Imperial College of Science and Technology, London) reviewed the treatment of gravity and magnetic survey data, where interpretations aim to deduce sub-surface mass distributions accounting for observed surface fields. Fundamental difficulties are ambiguity and lack of resolution. Ambiguity reflects dependence of the gravity anomaly on several factors, including form, size, depth and density contrast. When all these factors concerning a buried mass are known, it is possible to predict uniquely the effect on gravity at any point on the surface; but when interpreting a gravity profile recorded in a new area, the factors cannot be evaluated individually, and possible permutations allow many solutions consistent with the profile. Only geological control can limit the inherent ambiguities. Lack of resolution was illustrated by indicating that the interpreter cannot distinguish a point mass from a cube or sphere, since all produce similar gravity profiles. Depth to centre, however, can be computed with reasonable accuracy and an estimate of size is obtainable from the maximum of the anomaly, though it depends in turn on an estimate of density contrast.

Various numerical methods of analysis have been proposed, but Prof. Bruckshaw stressed that mathematical transformations cannot overcome limitations inherent in the original data, while subjective bias may be introduced in the process. As a preliminary step, it is usual to isolate local anomalies thought to represent shallow geological structures by removing a regional background corresponding to smooth average variations. Only rarely, however, can the regional be assigned geological significance, and the smoothed form assumed varies between different interpreters. Attention has been given to the second vertical derivative of gravity following claims of higher resolution from a fourth-power relation with depth as compared with the normal square law, and correspondence between zero contours of second derivative and vertical density boundaries. Unfortunately, precise evaluation of second derivatives requires continuous information whereas field observations are made at a series of discrete points. One process of analysis depends on the subjective drawing of smooth curves through available points. Alternatively, an interpolation formula may be applied, but developed formulæ give different solutions depending on size and form of primary grid. Final stages depend on comparisons with model curves, and it is important to derive these using the same grid. In reconnaissance of new areas, such methods are rarely warranted. No amount of mathematical analysis can remedy insufficient geological control, and if only geophysical data are available, interpretation always remains ambiguous. This was demonstrated recently in an example published by P. E. Jacobsen, of the Creole Petroleum Co., showing differences between two independent interpretations of a magnetic survey in eastern Venezuela. However, if good geological control is available and physical properties of the geological formations have been extensively studied, as in parts of England, some difficulties can be resolved and confident estimates advanced.

Dr. M. H. P. Bott (University of Durham) agreed that gravity and magnetic data are ambiguous, but felt that useful conclusions can generally be salvaged from the sea of uncertainty by applying simplifying assumptions legitimately drawn from geological knowledge of similar environments. The practical limit of interpretation is frequently determined by how far such reasonable assumptions permit assessment of background and isolation of the interesting anomaly from other disturbances. Once the anomaly has been isolated, total mass can be accurately evaluated by areal integration of the gravity contours. Russian work, recently developed further by Dr. R. A. Smith, shows that if only a few conditions are satisfied a unique solution may be possible. As an example, if an anomaly arises at a single interface across which the density contrast is constant and known, then the shape of the interface can be interpreted directly. Usually the limiting conditions are not accurately known but can be expected to lie within a certain range, and this information permits use of an uncertainty principle through the inequality theorems of Bullard and Cooper, later extended by Bott and Smith. Minimum and maximum values for depth to the source of the anomaly can be obtained. Limiting depth estimates can be derived also from second and third horizontal derivatives of the gravity anomaly, through formulæ of Dr. R. A. Smith relating maximum derivative and maximum depth. The limiting case, corresponding to a symmetrical truncated wedge-shaped body with each edge contributing equally to the derivative, can be modified for the situation where one edge is distant from the point of observation, as for measurements at the margin of an extensive body. Dr. Bott showed how, using this method, he had analysed profiles across the margin of the Weardale anomaly for an estimate of depth to the top surface of the postulated Weardale granite, afterwards proved (at a depth of 1,281 ft.) in a deep borehole at Rookhope, Co. Durham. Using maxima in second and third horizontal derivatives calculated from closely spaced observations by gravity meter and assuming density contrast of 0·2 gm./cm.^{3}, analysis had shown that the top of the postulated granite must lie at less than 3,500 ft. beneath Weardale. It is difficult to measure gradient maxima sufficiently accurately with a gravity meter, since an average over a base-line and not a point-value is

observed. Dr. Bott believes that the torsion-balance, little used recently, might be used advantageously.

Similar methods often prove satisfactory for deciding between alternative geological possibilities, as in distinguishing gravity lows over sedimentary basins from those due to granites. In the former case the boundaries of the lighter sediments slope in towards the centre of the anomaly, whereas the granite margins slope out at depth. Different amplitude ratios between derivative maximum and minimum flanking the anomaly are detectable, and contrasting results from gravity traverses crossing the margins of the Cheshire Basin and the Dartmoor Granite were displayed. Finally, useful results can be derived from comparisons with models, since modern digital computers will check quite speedily whether a postulated geological structure would produce the profile observed or whether marked divergences necessitate a new hypothesis. Dr. Bott concluded by saying that, applied to analyse magnetic data, these methods encounter added difficulties due to variations in direction of permanent magnetization.

Mr. G. Tait (Iraq Petroleum Co.) contributed a paper outlining the geophysicist's views on interpretation of seismic surveys. He remarked that recent instrumental developments aim at producing a greatly simplified presentation of results in the hope that by transforming a series of impulses into a variable density profile the main features of the geological structure may be comprehended at a glance. No method of presentation, however, alters the fact that the behaviour of the seismic wave depends on elastic constants in the rock formations concerned, and progress or difficulties in interpretation relate to whether and where variations in these constants occur. It is not always possible to predict from lithology, for seismic velocities in adjacent sandstones and limestones can be identical. Local velocity control is doubly important, because velocity discontinuities may not correlate directly with stratigraphic interfaces and because travel-time and velocity have equal weight in seismic determination of depth. Satisfactory velocity data can be obtained from well-shooting or by recording velocity logs in deep boreholes; but in virgin areas, where information must come from surface shots, available values may be inadequate. Accurate velocities can help when distinguishing between multiple reflexions and deep reflectors from curvatures in the moveout or by recognizing anomalous dips.

Several of these and other complications which the interpreter must disentangle were clearly demonstrated from oil exploration surveys by the Iraq Petroleum Co. One slide showed how tangential distortion against high-speed beds can simulate the indications of a natural structure. Importance of spread-length was apparent in the same example, since curvatures which could not be identified on a short spread became clearly visible at 12,000 ft. Records of a noise-spread indicated that alignments in background may confuse with weak reflexions. Profiles shot in the foothills of Iraq demonstrated both the problems and the importance of identifying multiple reflexions and diffraction cross-overs which may have amplitudes greater than those of the geologically significant events. Lower-amplitude contrast between events in a profile across the main producing oilfield of Iraq made it appear somewhat of an anticlimax, though containing important information. Mr. Tait's evidence made clear that, in dealing with seismic records, the interpreter must continuously bear in mind natural conditions under which the survey has been performed, velocity data available, instrument lay-out and complications which may have confused the records with multiple reflexions and diffraction effects.

Mr. A. N. Thomas (British Petroleum Co.) discussing geological factors in the planning and interpretation of seismic surveys, stressed the need for close co-ordination of geological and geophysical information. His first example, taken from the Po Valley, showed seismic reflexions on a phantom horizon to which geological information had been added, seismic evidence controlling the section as to fault zones and dips, while stratigraphical detail came from boreholes. Following examples came from south-west Iran, where initial interpretation difficulties with seismic refraction surveys were resolved when stratigraphical considerations correlated highest velocity with Middle Cretaceous Rudist limestone, not with the massive Asmari limestone 2,000–3,000 ft. above. Refraction arcs in the Lali Plain, starting from positions determined by surface geological mapping, directed attention progressively southwards to prove concealed Asmari limestone structures. In other British Petroleum Co. surveys across Agha Jari and Lali, surface dip observations by geologists in an area of disharmonic folding gave valuable checks on geophysical evidence about elevation of a concealed crest. In exchange, structural interpretation of the surface geological maps was aided by the geophysical information. Evidence from Iran showed that, by producing regional isopach and facies maps, the geologist can illuminate seismic interpretation wherever such variations control velocity or ability to act as a refractor.

The bearing of velocity anomalies on seismic interpretation was next considered using an example by D. C. Skeels from a Devonian reef oilfield in West Canada. Reflexion times at boreholes to the Lower Cretaceous gave a velocity map used for controlling the seismic data, and the final seismic depth-map agreed with later sub-surface information more closely than an earlier map based on reflexion times only. In more complicated conditions accompanying Reef limestones in Western Alberta, structure contour maps and seismic isochron maps may show different relationships on successive horizons. Causes are sometimes difficult to assess, but it is clear that seismic evidence must be checked against drilling data at all available positions and levels. Difficulties in correlating reflexion pulses with specific geological formations were illustrated in results obtained near Calgary by Dr. T. C. Richards, in which corresponding seismic peaks and troughs could be seen to change stratigraphic horizon in different parts of the area. The sections also showed how ideas about the structure of the area changed as various stages of drilling, seismic survey and further drilling were completed. This analysis indicated the tendency of the seismic interpretation to smooth out complications and inability to locate with certainty the top of the Palæozoic, which is the most important lithological break.

Mr. Thomas concluded by saying that too much should not be expected from a seismic survey. It cannot eliminate the need for sound geological investigation; both lines of approach are necessary. The seismic method cannot give a complete picture of sub-surface conditions in areas of complicated structure, and geologists should realize the limitations imposed by the nature of the method.

Opening the meeting for general discussion, Dr. Bullerwell recalled a remark of Prof. Bruckshaw that potential theory has been known a very long time and that in many fields interpretation shows no fundamental advance over the past fifteen years. Noting that during this period there has been increased use of systems like the airborne magnetometer for recording continuous profiles, he asked whether these removed some of the subjective elements mentioned. Prof. Bruckshaw replied that the subjective element remains in spite of such developments, due to the gaps between profiles and uncertainties in completing contours. Though coverage is improved, it is never complete. Dr. W. Domzalski felt that some views expressed had been unduly pessimistic. Even though interpretations might prove quantitatively in error, qualitative results obtained following an imaginative approach often lead to new discoveries. For reasonable success in interpretation it is also important to choose the geophysical method most suited to the geological problem. Even where no control information to guide the interpretation is available, the possible results may justify geophysical work as the most economical means of preliminary reconnaissance. On the question of economics, Dr. Bullerwell asked how soon during a survey should the results be tested by drilling. Mr. N. L. Falcon said that satisfactory exploration implies a balanced programme combining geology, geophysics and drilling. It is desirable to establish control, pursue the investigation comprehensively and not anticipate conclusions on the basis of too few results, but geophysical interpretation remains speculative until the key localities are drilled. Dr. T. C. Richards said that geophysical experiences in Canada emphasize the importance of early drilling control. A quantitative approach is essential throughout and second-derivative gravity maps have proved unreliable for this. Seismic methods must be introduced at a very early stage and have adequate geological and drilling control, especially in the Reef field, to overcome difficulties due to facies changes. Otherwise, occurrences of Reef limestone in limestone or local velocity anomalies, as at Swan Hills, Alberta, would not be recognized.

In closing the meeting the chairman remarked that personal experience often decides for one interpretation method rather than another. Perhaps a real advance during the past fifteen years is represented by pooling of experience through free discussion and improved publication of geophysical results. There is certainly a clear recognition of fundamental problems.

W. Bullerwell

TWELFTH INTERNATIONAL ASTRONAUTICAL CONGRESS

THE International Astronautical Congress is an annual meeting of the interplanetary societies of the world. Societies take it in turn to act as host, and the recent meeting, during October 1–7, in Washington, was the first occasion that the meeting had been held on the American continent. Next year's conference was fixed for Sofia, Bulgaria, it having been held in Stockholm last year and London in 1959. Of the 750 people registered, some 300 came from outside the United States. The president of the International Astronautical Congress this year was Academician L. I. Sedov, of the U.S.S.R., and for the forthcoming year Prof. J. Pérès, of France, was appointed the new president.

The week following the Congress was the occasion of a meeting in New York by the American Rocket Society—"Spaceflight Report to the Nation".

There was perhaps a feeling that the International Astronautical Congress was of not quite such a high technical standard as previous ones, as many Americans seemed to consider the American Rocket Society meeting to be the more important of the two—a view not altogether shared by the European delegates.

The opening ceremony on Monday was followed by a reception and buffet at the Bolling Air Force Base, where Dr. Theodore von Kármán was very much in evidence among the delegates.

The technical sessions started at 9 a.m. on October 3 with three simultaneous sessions on space propulsion, astrodynamics and guidance, and the Fourth Colloquium on the Law of Outer Space (the Third Colloquium was held in Stockholm in 1960).

The session on space propulsion had two lectures from British delegates, the first by Mr. A. W. T. Mottram (Bristol Siddeley Engines, Ltd., Coventry) entitled: "Propulsion of the Final Stage of a Satellite Launcher using Liquid Hydrogen as Fuel". Although this was the first lecture of the morning, it was well attended and there was a good discussion, although Americans in the audience were perhaps a little reluctant to describe some of their more recent failures in this field. It must be remembered that liquid hydrogen has not yet been used successfully to place a satellite in orbit, and that it was announced during the course of the Congress that the *Centaur* rocket using liquid hydrogen as a fuel has been officially set back eight months.

The other British paper, "An Examination of the Characteristics of Propulsion Systems for Inter-Orbital Transfer", by P. A. E. Stewart (Hawker Siddeley Aviation) was read in his absence by his colleague, Dr. W. F. Hilton. This described the more exotic forms of propulsion, including an omnidirectional method of focusing the Sun's rays for the direct heating of liquid hydrogen for use as a working substance.

Undoubtedly the most noteworthy paper of the morning was by another British delegate, Arthur C. Clarke (Clarke-Wilson Associates, Colombo), under the title "The Social Impact of Communications Satellites". This was presented during the Space Law Colloquium and attracted widespread interest. A future state of affairs where worldwide communications are as cheap and reliable as our present local communications was investigated, and its effects on social behaviour and trade were discussed. Mr. Clarke is, of course, well known for having started the idea of communications satellites by his article in October 1945 in *The Wireless World*, and indeed a reprint of this article was issued to all delegates.

The Space Law Colloquium continued in the afternoon and there was a session on energy conversion and yet another simultaneous session on astrodynamics and guidance. This last subject was treated as a round-table topic where a number of contributors made both prepared and unprepared comments, and included Prof. Zdenek Kopal (University of Manchester).

On October 4 the round-table concept was continued with a discussion on exploration of the solar system by radar and radio astronomy, the Moon and Venus being considered in the morning and Jupiter and future experiments in the afternoon. The radio reflexion experiments from the surface of the Moon appear to show fairly conclusively that much of the Moon is covered with a layer of dust having a thickness less than 1 cm. The session on Jupiter was of interest on account of the detailed description of the radio emissions from the Great Red Spot. The nature of these emissions is now fairly well established, but their cause appears to remain a mystery.

The most significant communication at the Conference was given by the Russian delegation, who revealed that their cosmonaut Titov was space-sick throughout the duration of his 24-hr. trip around the Earth, although this did not prevent him from sleeping in accordance with plans, or from carrying out routine duties which had been assigned to him.

On October 5 the weather was fortunately much better, and the now traditional conference boat-trip was made down the River Potomac past the Naval Research Laboratory's radio telescope, on to Mount Vernon. This informal occasion probably gives more opportunity for relaxed discussion between *ad hoc* groups of experts than is possible in the more formal atmosphere of the conference hall. The Congress banquet was held in the evening and was addressed by Academician Sedov.

On October 6 another British paper was presented, "Blue Streak as First Stage of a Satellite Launcher", by G. K. C. Pardoe. This described the present position of Britain's only large rocket, based on the design of the American *Atlas* rocket, which is the largest they have attempted to fire to date. No particular reference was made to possible British or European payloads, although possible European collaboration in the future was mentioned. Simultaneously, there was a round-table meeting on space communications, but most amazingly no reference was made to the use of radio, which is of course the obvious way for exploiting space for communications purposes. The signals to be conveyed would be modulated on to beams of light emitted from optical masers. This method gives a promise of tremendous band-width at some remote time in the future. Use of ultra-violet light for communications was proposed by Mr. J. W. Ogland, and one rather speculative paper suggested the use of γ-rays for communications. If the vehicle is propelled by a nuclear rocket, the γ-rays are available as a by-product and some form of hinged lead sheet has to be contrived for signalling purposes. This method is limited to use in space in the absence of any atmosphere and was shown to work at ranges up to 100,000 miles, but the signalling frequency is limited to one cycle per second.

Finally, on October 7, delegates were taken on a tour of the NASA Goddard Space Flight Center at Goddard, Maryland.

W. F. Hilton

THE VEHICLE DRIVER

A MEETING of the British Occupational Hygiene Society was held at the Traffic and Safety Division of the Road Research Laboratory during November 9–10. Six papers were read and discussed; for the first two, which dealt with bus drivers, the chair was taken by Dr. L. G. Norman, the president of the Society.

Examination by Dr. P. Froggatt of data from Northern Ireland revealed that a curve of accident-rate plotted against age of driver had a broad minimum over the ages 45–55 years which was due to the beneficial results of experience being opposed by the decline in performance with advancing age. The accident-rate of experienced drivers rose above 50 years of age.

Mr. C. J. Cornwall had examined the records of London bus drivers for the period 1957–59 for which the average rate was 1·37 accidents per driver-year on a mileage of about 14,000. Accidents were associated with traffic density. The accident-rate fell with increasing experience more rapidly than it rose with age; the fall was marked up to 47 years and slower up to 70. Replacements of old drivers by younger men would increase the number of accidents.

Dr. R. J. Smeed, deputy director of the Road Research Laboratory, occupied the chair during a session which was opened by Mr. W. Gissane, who described the nature and cause of injuries resulting from motor-car accidents in a city. Squadron-Leader D. I. Fryer told of the development of safety belts in aircraft, going back to Colonel Cody, who was the first man to fly a powered machine in England. The design and testing of modern safety-belts were described in detail, and the value of rearwards-facing seats, adequately attached to the airframe, was emphasized.

Road experience with safety belts was dealt with by Dr. A. J. Moreland, who approached the problem of assessing accidents quantitatively by defining a damage index. This number was evaluated from the damage to chassis, compartment and bodywork. When divided by the weight of the motor-car it correlated well with the difference between the squares of the velocities of the objects coming into contact.

The damage index divided by weight was used as a basis for comparing the frequency of casualties of various degrees. Fatalities commenced at a figure near 15 and rose steadily; serious injuries rose from near the origin while slight injuries attained a maximum at about 25.

Safety belts of good design, firmly attached, could prove beneficial, but there were suggestions that people drove faster when wearing them, and they did not check the forward velocity of the head on impact or protect it from objects flung forward from the rear. The steering arrangements, likewise, might either promote injury or provide protection.

The final paper was delivered by Mr. I. D. Brown with Prof. D. D. Reid in the chair. Observations of police and other skilled drivers had been used in an attempt to relate driving performance to fatigue and distraction. It seemed likely that there was spare capacity to draw on in case of need and that fatigue from general occupations before driving might be more serious than that induced by driving. Tests of distraction by using tape recordings in which the subject was either interested, or not interested, were also carried out.

The Road Research Laboratory demonstrated the telemetering of movements of the controls of a vehicle under way, of recording what happens in an accident and of experimental collisions. The incorrect basis of

early tests on motor-cycle crash-helmets was shown and specimens illustrated the protection afforded by helmets and the distribution of the injuries of motor-cyclists.

The bulk of the meeting was concerned with the results of accidents and diminution of their effects on people; little attention was given to the prevention of motor-car accidents by methods within the control of the vehicle driver. The papers and discussion will be published in the *Annals of Occupational Hygiene*.

C. N. Davies

MECHANISMS OF VIRUS INFECTIONS

A DISCUSSION meeting of the Royal Society, arranged by Prof. Wilson Smith, on the subject of "Mechanisms of Virus Infections", was held on November 2. Owing to the large numbers attending, the meeting was transferred, by courtesy of Sir Lawrence Bragg, to the lecture hall of the Royal Institution. The president of the Royal Society, Sir Howard Florey, took the chair.

In his introduction, Prof. Wilson Smith traced briefly the progress of virological knowledge from the early almost metaphysical questioning into the nature of viruses to the present wealth of information regarding their chemical constitution, structure and intracellular behaviour. He wondered, however, whether these particular aspects were not in danger of being over-emphasized at the expense of more traditional problems relating to virus disease. The natural history of any virus disease is intimately related to the survival cycle of the virus concerned and, in the metazoon host, this cycle is necessarily complex. The route of infection and primary lodgement, paths and mechanisms of spread through the host, replication and ultimate release must be considered at the various levels of the cell, the intact host and the host population. It was with this in mind that the present programme had been built up around the concept of the survival cycle.

Prof. A. W. Downie (University of Liverpool) opened the discussion with a paper on "Mechanisms of Virus Entry and Spread within the Host (Animal Viruses)". Although a rapid survey of the various routes of infection known to occur was given to illustrate the extent of the subject, and problems associated with the question of neural spread in such diseases as poliomyelitis, herpes and pseudo-rabies were briefly discussed, the paper was centred on the pathogenesis of disease in the pox group of viruses. Fenner's detailed work on ectromelia has laid a pattern which serves as a standard of reference for investigations with other members of this group, and a study of the highly lethal rabbit pox infection shows that it follows the same general course. The main difference is that the stages of primary and secondary lodgement with final involvement of the skin, and of primary and secondary viræmia, are less well defined in rabbit pox than in mouse pox. Despite thorough investigation of animals infected by the intra-nasal route, no primary lesion is identifiable although virus can be readily demonstrated in the tissues of the nasal passages and trachea. The blood contains virus as early as the second day after infection and thereafter remains positive. Clinical disease develops on the fourth day. The finding that provoked the greatest interest and discussion was that animals do not become infectious by contact until the fifth or sixth day, at least 24 hr. after the onset of clinical disease, a finding closely similar to that in human smallpox. Following intranasal infection, virus may be isolated from the tissues of the upper respiratory tract in rabbit pox, and smallpox virus is presumed to invade by this route in the majority of human cases. Why then is the patient not infective during the incubation period? Dr. C. H. Cadman (Scottish Horticultural Research Institute) dealt with the same subject in its relation to plant viruses and pointed out that there is an essential difference in the problems involved, since plant viruses are unable to effect entry into the tissues without external aid. Trauma is an essential prerequisite to infection and is usually inflicted in Nature by insect vectors. In the laboratory the necessary damage is achieved by rubbing the leaf, but the inefficiency of this procedure may be gauged from the fact that about 10^6 infective particles are necessary in order to produce a lesion. Further, since the plant does not possess conveniently isolated internal organs which can be segregated by dissection and to which the virus can track, spread of virus cannot be followed as in the animal host. It is probable that virus spreads in the translocation stream, but if so the form of the virus at this time is not known. Since certain viruses are apparently capable of dispensing permanently with their protein coat, it is possible that spread within the plant occurs in the form of ribonucleic acid. The possible role of plasmodesmata and the problem presented by the fact that virus appears to spread through callus tissue cultures just as fast as through intact plant tissues were also discussed.

It was clear from both these papers, in their different contexts, that there is a long way to go before the problems of virus invasion of host tissues can be considered to be satisfactorily explained.

"Intracellular Replication Mechanisms" were discussed by Prof. M. Stoker (University of Glasgow), who considered the subject from the point of view of the interrelationship of virus growth to cell growth. The types of interrelationship exemplified by bacteriophage infection are: (1) the extreme virulence found in the *T*-even phage where adsorption of the protein coat is sufficient to cause immediate death of the cell with breakdown of deoxyribonucleic acid; (2) intermediate virulence where the host cell is not immediately killed but cell division is prevented; and (3) the avirulent prophage relationship. In the case of animal viruses, infection usually results in death of the cell, and the difficulties in demonstrating non-cytopathic infection of cells were discussed in detail. For proof it is necessary to study isolates of single cells and demonstrate, first, release of virus and, second, cell division in that order.

Prof. Stoker concluded that there is as yet no satisfactory evidence for infections of this type with normally cytopathogenic viruses, but this has recently been acquired by Rubens with the Rous sarcoma virus so that this virus, which is not normally cytopathogenic, is the only one for which the formal criteria have been satisfied. In the case of polyoma virus, either cytopathic effect or cell transformation may follow infection *in vitro*; but in the latter case, it has not proved possible to demonstrate virus in the

transformed cells and these remain super-infectable with polyoma virus, albeit with difficulty. It must be concluded that persistence of the virus is not necessary for these cells to retain their character once transformation has occurred.

Thus three types of non-cytopathogenic relationship appear to be possible. In the case of the Rous virus both virus and cell multiply with the intermittent release of infective virus; in lysogenic bacteria both multiply together but virus is not released without induction and death of the cell occurring, and finally with polyoma the virus may induce a cell transformation without itself persisting.

Dr. A. Isaacs (National Institute for Medical Research) considered "Interference Phenomena" as a further aspect of intracellular behaviour. Many interference phenomena have now been shown to be mediated by interferon, and the properties of this substance were described. It is a protein of molecular weight 63,000 which is produced by all vertebrate tissues so far tested. All viruses examined have been found to provoke production of interferon and all are to some extent susceptible to its action. In its protective action it possesses some specificity for the species in which it is produced. It is non-toxic at viral inhibitory concentrations and does not inhibit cell division. In infected cells it suppresses the production of viral nucleic acid, possibly through its inhibitory activity against oxidative processes providing the energy for synthesis. As might be expected, therefore, it is found that viruses depending on oxidative processes for their replication are more strongly inhibited than those which do not have this dependence.

The possible role of interferon in recovery from virus infections was discussed and some interesting speculations added on the possibility that the action of interferon in virus infections is incidental to its role in the normal cell. Dr. Isaacs suggested that its function might in fact be that of excluding extraneous ribonucleic acid of whatever nature. It is not formed during the first third of chick embryonic life when ribonucleic acid might be acting as a vital intermediary in the processes of morphogenesis, but thereafter is formed in increasing amounts in response to the appropriate stimulus. It might be that its formation in later embryonic life is a mechanism for the protection of the tissues from unwanted morphogenetic stimuli. This suggestion aroused some argument and it was pointed out that interferon does not exclude viral ribonucleic acid from the cell but apparently suppresses its formation.

The last paper on cellular relationships of virus was given by Prof. G. Belyavin (University College Hospital Medical School, London) on "Latency in Virus Infections". Prof. Belyavin treated the subject from a purely theoretical point of view and demonstrated by means of a mathematical model that in any system where persistence of infection depends on a balance between the rate of replication of virus and the rate of replication of cells, an impossibly critical state would exist. Such a system would inevitably lead either to the virus gaining the upper hand with eventual destruction of the whole cell population, or to cell multiplication outstripping virus multiplication with the elimination of the latter. The assumptions on which the model was constructed did not include variation in the susceptibility of the cell population or the role taken by such substances as interferon. The intervention of some such factors would be essential if a stable balance between virus and host cells were to be achieved.

Epidemiological factors in relation to animal and plant virus diseases respectively were presented by Prof. F. J. Fenner (Australian National University) and Dr. L. Broadbent (Glasshouse Crops Research Institute). These two papers provided an interesting comparison of the problems in these two fields, the more so as Prof. Fenner confined himself to a discussion of myxomatosis, a vector-transmitted disease. A comparison of the Brazilian, Californian and Australian viruses in rabbits native to those regions suggests that, in the establishment of the disease in Nature, natural selection acts not on the virus as such but on the factor of transmissibility. Thus the three types of virus are capable of infecting the Californian rabbit *S. buchmani*, but whereas the attenuated Australian strain fails to give detectable virus in the skin lesions and the South American strain gives a titre of only 10^4/gm., the Californian virus achieves a titre of 10^8/gm. and only the last is found to be transmissible by mosquitoes. In Australia since 1952, the original virus, which killed close on 100 per cent of infected animals, has been largely replaced by less virulent variants. The fall in mortality has not, however, been extreme or progressive, and the dominant strains have for some years remained in the 'grade III' category in which mortality is about 90 per cent; but since the infected rabbits live longer, the virus is available for transmission for a period of about 15 days as against 5 days with the highly virulent strains. However, the increase in the numbers of genetically resistant rabbits may ultimately favour the more virulent virus.

The highly complex interplay of factors governing the epidemiology of myxomatosis was reflected in the field of plant viruses. Dr. Broadbent dealt with the epidemiology of plant virus diseases in wider terms, but the main interest in his paper lay not in the artificial spread of viruses by human agency or even by contact, but in the intricacies governing its transmission by vectors. While the nature and static habits of plants eliminate the complications arising from behaviour patterns, they equally introduce factors specific to plant epidemiology. Thus, while it is easy to understand that the size of plants and their position relative to each other and to sources of infection external to the crop must influence spread of infection, the results of the microclimate within the crop are more subtle. If plants are closely spaced, the transfer of vectors will be facilitated; but this may be offset by the development of temperature and humidity conditions within the crop which are not tolerable to them. The vector will then be confined to the new shoots which may contain little virus. Similarly, plants are in general more susceptible to infection when young, so that climatic influences on the time of greatest prevalence of the vector may determine whether or not infection is widespread irrespective of whether the vector is particularly numerous. Despite these factors, which have no real counterpart in the animal virus field, there are more similarities than differences apparent in the epidemiology of plant and animal viruses and Dr. Broadbent's paper served to illustrate some of these. For example, some viruses, such as potato virus *Y*, can be picked up in a few seconds feeding and immediately spread to uninfected hosts. These viruses do not persist in the vector for more than a few hours. Others, such as potato leaf roll, require prolonged feeding to infect the vector, cannot be transmitted before the lapse of a latent period, and thereafter persist in the vector

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for many weeks. This contrast is very similar to that between myxomatosis and yellow fever.

Finally, the damage which virus infection inflicts on the host was discussed by Dr. J. C. N. Westwood (Microbiological Research Establishment, Porton) in relation to the intact host and by Dr. Alison Newton (University of Cambridge) at the cellular level. Dr. Westwood discussed "Virus Toxicity" and its possible role in the production of disease and ultimately death in fatal virus infections. The term 'virus toxicity' was originally coined to cover the production, by massive doses of virus, of lesions or death in susceptible or non-susceptible animals without the occurrence of multiplication of the virus. The toxic factor has always been inseparably associated with the virus particle itself. Since virus disease is normally initiated by small doses of virus and accompanied by multiplication, it has seemed unlikely that 'toxicity' could be involved; and the latter has always been regarded as a freak laboratory phenomenon unassociated with production of disease. It was suggested that this concept might be wrong. Experiments were described which showed that the toxicity of rabbit pox virus is associated with a partial cycle of replication, as is the toxicity of other viruses in which such partial cycles have been sought. Death in rabbit pox is preceded by the abrupt onset of shock, with some evidence of increased capillary permeability, and the clinical picture can best be explained by the presence of some toxic factor in the blood. During the four days preceding death in acutely fatal infections, the virus concentration in the blood may rise to as high as 10^8 infective units/ml. and similar concentrations occur in fatal smallpox and herpes infections in man. The cytotoxic effect of such virus concentrations on the capillary endothelium could be the cause of the increase in capillary permeability and so precipitate the animal into shock. Since no toxic factor other than the virus has ever been demonstrated to result from cell-virus interaction, the possible role of direct virus toxicity in disease must be seriously considered.

Damage to the intact host depends on the damage produced at the cellular level, and Dr. Newton considered the "Biochemical Aspects of Virus Infectivity" in relation to modification of cellular metabolism. The main modifications are found first in the production of new virus and second in changes in the nucleic acid and protein synthesis. Viruses which multiply in the cytoplasm make less use of the cell metabolism—for example, vaccinia virus does not affect the metabolism of deoxyribonucleic acid—and such viruses probably produce their damaging effects by competition for metabolites. Those which multiply in the nucleus produce a more profound effect, since they must not only compete for metabolites but must also overcome the normal control processes of the cell. Thus pre-labelling of the cellular deoxyribonucleic acid with tracer thymidine shows that herpes virus causes a rapid breakdown of cell deoxyribonucleic acid probably due to increased deoxyribonuclease activity similar to the increased ribonuclease activity stimulated by poliovirus. It also stimulates synthesis of deoxyribonucleic acid. These changes must damage the control mechanisms of the cell, and interfere with synthetic activities in the host. In some viruses, such as encephalomyocarditis, viral ribonucleic acid is elaborated in the nucleus and protein in the cytoplasm. It is probable that in these instances cytoplasmic protein metabolism is governed by viral ribonucleic acid which migrates from the nucleus. The production of cell damage does not depend on completion of the multiplication cycle of the virus; for example, with poliovirus, herpes and rabbit pox viruses, inhibition of infective virus production does not prevent cell destruction. It was suggested that cell damage results from the release of lysozomes, disruption of the controlling mechanism of the cell, competition for metabolites and disturbance of metabolic balance.

The meeting was successful in provoking lively discussion and considerable disagreement on nearly every point raised by the main speakers. Dr. Sanders, in summing up, congratulated the participants on avoiding all reference to infective nucleic acids, and he also stressed the gulf which still exists between academic virology and virology as applied to disease.

J. C. N. Westwood

COTTON-GROWING IN NIGERIA

Agricultural progress relies on the pure sciences, on engineering and on economics. These cannot come into play until major practical problems have been resolved into their scientific components. Resolution is one of the functions of husbandry investigation. Recognition of the nature and importance of this function has come only within the past three decades. In this same period the other function of husbandry investigation has also been developed, namely, improvement of accepted practices in raising crops and livestock. Cultivations, drainage, sowing, grazing, housing of stock and other day-to-day matters were not looked on, formerly, as problems amenable to study: they were matters for the farmer's experience and tradition. Modern husbandry investigation seeks to improve all working practices by studying their underlying purposes and interpreting their effects.

That physical environment is primarily important for agriculture is now an axiom, though some costly flouting of it is yet fresh in memory. It is largely through husbandry investigation that scientific attention has been brought to its present intensity in such matters as rainfall characteristics, solar radiation, air temperature, shade, wind and moisture-holding capacity of soils.

Some highly successful husbandry investigations on cotton have recently been reported* from the Ministry of Agriculture Research Station at Samaru, Northern Nigeria.

Past work at the Station and in its area of interest had revealed a discouraging situation. Local yields were 150–200 lb. of seed cotton an acre. Late sowing partly accounted for this, but earlier sowing in experimental plots gave only 240 lb. Assisted by fertilizers and by early planting the maximum yield was 600 lb. At these yields insecticidal protection did not pay. Yield in a bad year was only half of that in a good one and in any small field good and bad patches markedly influenced growth and yield. An improved variety of cotton, bred at the Station,

* Lawes, D. A., *Emp. J. Exp. Agric.*, **29**, 116 (1961).

showed but a poor increase in yield (its merits were made clear in later trials under improved conditions). A belief had therefore grown up that the attainable yield of rain-grown cotton in the area was decidedly lower than that for other African territories.

Rainfall (total and effective) appeared to be the dominating factor for yield, and experiments were made during 1957–59 to assess its influence. From meteorological records and observations, 40 in. was deduced as the expected (1 : 1 chance) annual rainfall, 27·4 in. of which would come after July 1; and under local conditions a crop of cotton would need about 25 in. of rain in the growing season if growth was not to be limited by soil moisture (July 1 is recommended as the sowing date for cotton, as the earliest which allows food crops to be planted first). What happens to rain after reaching the soil and how control of this influences yield were the primary issues in the field experiments.

Surface 'capping' through heavy rain, to which the local soils are specially prone, was shown to be largely controllable by timely hoeing and by mulching, entry of rain into the soil being thus greatly increased. The land is ridged for cotton and other crops, and it was found that here, as elsewhere, water conservation could be improved by 'tying' the ridges with small bunds at intervals along the furrows. In dry years this considerably increased yield but depressed it in wet years. These effects were clearly interpreted by soil–moisture profiles.

The effects of varying degrees of these controls having thus been measured, field trials were arranged, having in mind steps which could be fitted into peasant practice. A light mulching, in the furrow bottoms only, proved effective, and by slitting the furrow bottom and working a small amount of mulch into the slit the effect was enhanced. Tying alternate ridges only worked well, and avoided yield depression through standing water in wet years. Groundnut shell, dead grass and chopped *Sorghum* stalks made good mulches, the shell being best. By preparing the land for sowing at the onset of the rains, instead of just before sowing, which is local practice, cotton yields were raised by 15 to 20 per cent in two trials. Increased penetration and retention of rain had evidently been secured. Good response to fertilizers was obtained where tied ridges and mulch were also used.

The practical inference was clear—fertilizers, insecticidal protection, improved varieties and other betterments are repaid only when water conservation is amply ensured and this is practicable at peasant husbandry level. To drive the lesson home, cotton was grown on a half-acre plot for four years running in which rainfall was 55, 35, 42 and 43 in. Yields were all of the order of 2,000 lb. of seed cotton an acre, which is good for rain-grown cotton anywhere and excellent in comparison with any other part of Africa. Moreover, picking was ended by Christmas whereas it dawdled on for another 2–3 months on other plots.

This successful husbandry investigation is of more than local and immediate value. It is part of the widespread studies of rainfall, soil moisture and crop water needs carried out by the Empire Cotton Growing Corporation. The basic work is done at its Central Research Station, Namulonge, Uganda. All this work deals not with cotton alone but also in conjunction with the customary food crops of cotton growers. Agriculture in general is thus benefited in cotton-producing countries. Moreover, the practical problems centring on rainfall are becoming so defined and resolved as to enable their deeper, physiological study to be effectively opened up. Plant breeding, also, gains a clearer sense of direction.

F. L. Engledow

RADIOMETRIC AND PHOTOMETRIC STANDARDS

TWO recent publications in the series *Notes on Applied Science* of the National Physical Laboratory, Teddington, illustrate some of the activities of the Light Division of the Laboratory.

No. 23 in the series[1], *Radiometric Standards and Measurements*, by E. J. Gillham, deals with the methods used at the Laboratory for the measurement of ultra-violet, visible and infra-red radiation. The contents consist of three main sections devoted to the measurement of total radiation, the measurement of monochromatic radiation, and the absolute measurement of radiation, respectively. Total radiation is usually more intense than monochromatic radiation and therefore can be measured more easily, but the total energy content of a beam of radiation is often of less practical significance. An instrument for measuring total radiation must be equally sensitive to radiation at all wave-lengths, and the only means of converting radiation into another form of energy with predictable efficiency over the whole wave-length range is by absorption at a blackened surface, that is, to use a thermal detector. Fortunately, blacks with an absorption factor of 95 per cent or more over the whole spectral range of interest are available, and consequently thermal detectors with an error due to selectivity of not more than 2 or 3 per cent can be obtained. The type of thermal detector commonly used is the thermopile, and in the booklet the Moll thermopile, which has stable characteristics and which forms a very useful working standard for measuring radiation or for calibration of other radiation detectors, is described in some detail. A set of six Moll thermopiles is maintained at the National Physical Laboratory for calibration purposes. The methods used for the intercomparison of thermopiles and for the accurate measurement of the selectivity of a thermopile using a Callender radio-balance and three different sources of radiation are discussed.

To illustrate the problems encountered in the measurement of monochromatic radiation a description is given of a routine test undertaken at the Laboratory to determine the special sensitivity of a photoemissive cell, in the 0·25–0·7μ wave-length range. The optical arrangements and apparatus required for the measurement of the spectral sensitivity, and also the absolute sensitivity of the photocell, are given. For the absolute measurement of radiation a thermal detector in which the target is provided with a resistance element or other means for supplying a measurable amount of electrical power is recommended. At the National Physical Laboratory the absolute radiometer used is the Guild drift radiometer. It is of the compensated type with

two similar receivers, the front one of which is exposed to the radiation. The target consists of a massive copper disk 4·5 cm. in diameter and 0·5 cm. thick to ensure temperature uniformity. Thermocouples are attached at a number of points in order to average the rise in temperature. The electrical heating element is cemented to the front disk on the side exposed to the radiation. The cycle of operations and the practice carried out in the Laboratory for the calibration of working-standard thermopiles against the Guild radiometer with a radiation source, consisting of a 1,000-W. tungsten lamp operated at a colour temperature of 2,850° K., together with water filter and heat-absorbing glass to absorb radiation of a wave-length longer than 1μ, are explained in detail.

The second booklet, No. 24 (ref. 2), is concerned with photometric standards and the unit of light. The development of light sources from the early nineteenth century and the evolution of the present primary standard, with the internationally accepted unit of luminous intensity, the candela, are discussed, followed by a detailed description of the procedures carried out at the National Physical Laboratory with regard to the arrangement of the primary standard, and calibration of secondary standards of luminous intensity and luminous flux. Finally, the present international situation with regard to intercomparisons of photometric scales is reviewed, and a table is given showing the relative magnitudes of the candela (2,042° K.) as found in the most recent determinations (up to 1957) at various national laboratories. The monograph can be recommended as a comprehensive and instructive statement of photometric standards and light sources, and should be of value to all concerned with illumination. S. Weintroub

[1] Department of Scientific and Industrial Research: National Physical Laboratory. Notes on Applied Science, No. 23: *Radiometric Standards and Measurements*. E. J. Gillham. Pp. iv + 23. (London: H.M.S.O., 1961.) 1*s*. 9*d*. net.

[2] Department of Scientific and Industrial Research: National Physical Laboratory. Notes on Applied Science No. 24: *Photometric Standards and the Unit of Light*. J. S. Preston. Pp. iv + 32 + 4 plates. (London: H.M.S.O., 1961.) 3*s*. net.

GEOLOGY OF BROWN CLEE HILL AND THE ADJACENT AREA

*THE Old Red Sandstone of Brown Clee Hill and the Adjacent Area**, recently issued by the British Museum (Natural History), is an important paper as it deals with a classic area in which is displayed the most complete sequence of Old Red deposits of the Anglo-Welsh development. In the first quarter of the century Wickham King established a general stratigraphical succession for that development, which he based to a large extent on his findings in the Brown Clee district, but his supporting palæontological evidence was too meagre and scattered to provide really convincing fossil zones. At that time too many of the forms had been inadequately described or named from fragments. King's work, however, generated a stimulus that has led to a revolution in our knowledge of the British Old Red ostracoderm faunas. This has been the result of systematic collecting and accurate description. The latter we owe chiefly to the senior author, Dr. E. I. White, and Part 2 of the present paper is his latest contribution to the subject. While our knowledge of the fossils has been gradually accumulating, the palæontologist has had, to a great extent, to rely on King's stratigraphical conclusions, which were not always based on reliable mapping.

In the present case the two junior authors have presented an excellent map based on accurate 6-in. survey and elaborate collecting, which have enabled them to determine the range of the fossils with considerable accuracy. For the Downtonian Series, they have taken advantage of much recent palæontological work; and the zones for this series can now be regarded as well established, and their evidence as merely confirming conclusions reached previously in this and other areas. But for the desperately barren Dittonian and Clee Series, their painstaking field-work has supplied Dr. White with material, by which broad zones can now be defined with some exactness.

Part 1, devoted to the stratigraphy, includes interesting discussions concerning the geographical conditions governing sedimentation, the ecology of the fossiliferous 'pockets', the so-called *Psammosteus* Limestone (which has never yielded a fossil, let alone a *Psammosteus*), and foreign pebbles in the conglomerates; but its main significance is the correlation of the fossils with the stratal succession, and the determination of the range of each important species. A valuable feature is a list of more than a hundred localities with the fauna discovered at each.

Part 2 is descriptive of a number of new species and varieties illustrated by 60 text figures and 16 plates. Of particular value are the new forms discovered by the authors and others in the Clee Series and in the unconformable upper Old Red beds (the Farlow Sandstone Series). L. J. Wills

* Bulletin of the British Museum (Natural History). Geology. Vol. 5, No. 7: *The Old Red Sandstone of Brown Clee Hill and the Adjacent Area*. 1: Stratigraphy. By Harold William Ball and David Lawrence Dineley. 2: Palæontology. By Errol Ivor White. Pp. 175–310 + plates 33–48. (London: British Museum (Natural History), 1961.) 70*s*.

FIRE RESEARCH 1960

THE recently issued annual report of the Joint Fire Research Organization* records the bringing into use, during 1960, of new buildings providing 30,000 sq. ft. of permanent floor area for the continued prosecution of fire research (see *Nature*, 189, 105; 1961).

Among the many investigations described, that which focused attention on the behaviour in draughts of oil heaters of the drip-feed radiant type has doubtless aroused the greatest public interest. The relatively new and unique wind-tunnel facilities of the Fire Research Station permitted an expeditious study of this problem, followed, within the year under review, by the publication of a report and a new British Standard and, finally, by the introduction of appropriate legislation.

* Department of Scientific and Industrial Research and Fire Offices' Committee Joint Fire Research Organization. Fire Research, 1960: *Report of the Fire Research Board with the Report of the Director of Fire Research*. Pp. viii + 67 + 12 plates. (London: H.M.S.O., 1961.) 5*s*. 6*d*. net.

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Of particular scientific interest is the large programme of work now in progress on the quantitative aspects of fire in structures, both real and idealized. A particular object of this is to establish scaling laws for rate of burning, size of flames and the spread of fire by heat transmission from them, and the disposal of smoke by ventilation.

The statistical inquiries, as always, are interesting, and this year include reference to the incidence of fire in post-war houses, fires caused electrically, and aircraft crash incidents. Tests have been carried out on the relative effectiveness of audible warning devices in traffic, from which the traditional fire bell emerges rather badly. Preliminary experiments on the use of a gas turbine as an inert gas generator for extinguishing fires in large building spaces have given encouraging results. Fire-resistance testing of building materials, work on the prevention or mitigation of gas and dust explosions, and a number of other projects have been continued. J. H. BURGOYNE

PROGRESS OF CANCER RESEARCH

THE annual report of the British Empire Cancer Campaign continues to expand year by year; the thirty-eighth edition* is a massive book of nearly 800 pages, the scientists working either wholly or partly under the ægis of the Campaign number nearly 1,500, and a million pounds was spent on research in 1960.

Some idea of the trends of cancer research, as described in the report, can be suggested by breaking down, into subject-matter and class, the total of papers published in 1960 by these investigators and comparing the resulting catalogue with that for 1950; the papers will, of course, represent the work more or less completed before 1960 rather than the present progress, but the main lines will undoubtedly remain substantially the same (Table 1). The table shows that in the ten years the trend has been to increase the volume of work on biochemical themes at the expense of carcinogenesis and radiobiology, and that the immunological and statistical approach is attracting more research.

Only a little of the large amount of research work detailed in the report can be referred to here. One of the most interesting investigations continues to be on the Gross leukæmia-inducing virus and the related polyoma virus. Miller confirms that removal of the thymus in *C3Hf/GS* mice at 3–4 months after they have been neo-natally inoculated with the Gross virus prevents the development of lymphocytic leukæmia which otherwise appears in 100 per cent of such inoculated mice. Grafting isogenic thymus into the thymectomized mice restores the growth potentiality of leukæmia. *C3H* mice which had been made tolerant to tissue from *Ak* mice at birth were inoculated with normal *Ak* thymus and became leukæmic; transplantation tests showed that the lymphocytic neoplasm arose from host cells and not from the inoculated *Ak* cells, thus demonstrating that a non-cellular factor from *Ak* thymus is a necessary component in the origin of this lymphocytic leukæmia.

C3H mice injected at birth with the Gross virus were later given a lethal dose of radiation and protected with normal isogenic marrow from untreated mice; most of the injected mice developed leukæmia, and tests with protecting cells carrying a marker chromosome indicated that the leukæmogenic virus is not only radio-resistant but is also resistant to any immune attack that might have been exerted by the protective marrow cells, and therefore there is not much hope of treating leukæmias of viral origin by total-body irradiation and marrow replacement.

Ambrose and colleagues, in experiments on normal and malignant cells grown *in vitro*, conclude that "The characteristic properties of the tumour cells so far suggested in the present studies are therefore as follows: (1) the tumour cell membranes show reduced mutual adhesiveness as compared with normal cells; (2) several lipases and phospholipases are more toxic for tumour cells than for normal cells and the tumour cells are also more sensitive to lipid in the medium, suggesting that more exposed lipid is present on the tumour cell membrane; (3) the structure of the tumour cell involves a less basic protein than the normal cell, suggesting a more acidic micro-climate at the cell surface, in agreement with the electrophoretic studies indicating an increased negative surface charge".

The possible cancer risks attached to the use of œstrogen implantation in cattle and poultry is the subject of a report by Sir Charles Dodds: "There has been a new interest in the alleged carcinogenic action of œstrogens during the past year. The widespread use of stilboestrol and hexoestrol in agriculture has generally been approved by governments. Stilboestrol implantation in poultry for the purpose of caponisation has become almost universal and it is also estimated that a very large percentage of meat produced in the North American continent has been produced under the influence of stilboestrol, hexoestrol or some similar substance. There has been a change recently in the administrative outlook in the North American continent on the use of these substances and at the present time, in America, their use has been banned by what is known as the Delaney Amendment to an Act in the F.D.A. This whole question is being looked into and we have been particularly interested in attempts to assess the intake of œstrogens in a normal diet. This aspect of

Table 1. PAPERS PUBLISHED ON CANCER RESEARCH

Classification	In 1960	Total in 1960 (per cent)	In 1950	Total in 1950 (per cent)
Radiobiology; radiotherapeutics; physics; tracer studies	187	21	79	33
Biochemistry of DNA, RNA, proteins; enzymes; carbohydrate metabolism	177	20	33	14
Clinico-pathology	105	11·9	20*	8·3
Cytology; tissue culture; electronmicroscopy; cytochemistry	87	9·9	19	7·9
Carcinogenesis; carcinogens; biology of tumours	81	9·2	38	16·0
Cancer chemotherapy; cytotoxins	70	7·9	15	6·2
Hormones; steroids	54	6·1	12	5
Immunity; immuno-therapy; transplantation	50	5·8	4	1·7
Mutation; cytogenetics	25	2·8	5	2·1
Statistics; geographical pathology	26	2·8	1	0·45
Viruses	21	2·4	6	2·5

* Report of Clinical Cancer Research Committee.

* British Empire Cancer Campaign. Thirty-eighth Annual Report covering the year 1960. Part 1: The Chairman's Statement and the Accounts. Pp. xxxviii. Part 2: The Scientific Report of the Researches undertaken by the Central Organization and its Autonomous Councils in the United Kingdom, and by some of its Affiliated Organizations Overseas. Pp. xxxix–lviii + 792. (London: British Empire Cancer Campaign, 1961.)

the problem seems to have been entirely overlooked by the legislators. There is, therefore, a renewed interest in compounds of the flavone and isoflavone series described later in this report".

Salaman and co-workers find that new-born mice are highly sensitive to carcinogens; after one year, of 26 mice of the '101' strain which had received 30μ of dimethylbenzanthracene neo-natally, 9 developed leukæmia, 25 lung adenoma, 7 skin papilloma and 16 papillomas of the forestomach.

Cunningham and colleagues at the Royal College of Surgeons have been studying cytologically the process of liver cancer induction by dimethylamino-azobenzene using a technique of section cutting which permits the life-like preservation of cellular structures in that mitochondria, free lipid, lipid-protein bonds and dehydrogenases are retained intact; the tissue being sectioned at $-25°$ after cooling to $-70°$.

Orr has been continuing his work on the chemical induction of mammary cancer in the mouse; such tumours did not develop in female mice of the *C57B1* strain after painting the skin with dimethylbenzanthracene (DMBA)—a standard technique—but if the females were made pseudo-pregnant by being caged with vasectomized males and then painted with DMBA, 21 out of 29 mice developed breast tumours due to the added stimulus from progesterone in pseudo-pregnancy.

Orr and Mandl find that senile virgin rats are very liable to spontaneous mammary tumours; of 69 such females aged between 600 and 1,200 days, 34 (49 per cent) showed macroscopic fibroadenomata, while a parallel series of 46 female rats used for breeding had an incidence of only 4 per cent mammary tumours. "It is tentatively suggested in the light of these observations that continuous secretion of œstrogen by virgin animals, uninterrupted by phases of progesterone secretion during pregnancy, stimulates the anterior pituitary. The œstrogen-stimulated pituitary secretes appreciable quantities of luteotrophin even before it becomes enlarged, at the same time output of other gonadotrophins decreases. The secretion of luteotrophin would account for both the mammary hyperplasia and the presence of excessively large corpora lutea. Absence of corpora lutea could be explained by insufficiency of LH with failure of rupture of Graafian follicles".

Baldwin, at Nottingham, finds that a commercially available motor-engine oil additive is highly carcinogenic for mouse skin; it consists of a mixture of compounds which include lead naphthenate, carbon tetrachloride, 1,1,1,-trichloroethane and a petroleum oil base; the indications are that the active factor is present in the oil base.

King, Hughes and Louis at Melbourne, in interesting work on the fluorescein conjugate staining of tissues, state: "The studies of the last four years have been continued and extended. In addition to serum globulins, serum albumin has been conjugated with fluorescein and rhodamine. The differential avidity of the dye for serum albumin as opposed to globulins has been confirmed. In addition, sera from species other than those previously examined have been investigated with similar results; normal tissues of all species studied stained but malignant tissues failed to stain.

"Tissues grown in tissue culture show the staining and fluorescence characteristic of normal tissues for the first three days. By the fourth day staining becomes patchy and subsequently no staining can be obtained, that is, after the fourth day the culture shows the same staining characteristics as malignant tissue. This conforms with observations made on re-introduction of such tissues into the original animal or one of the same species, when they grow in the same manner as true neoplasms".

In Melbourne also, Trautner and Coats have been using an ingenious technique in the study of species immunity to cancer; mouse ascites carcinoma cells were suspended in nutrient fluid in 'Perspex' chambers (0·1 ml.) fitted with non-reactive 'Millipore' filters of pore size 0·6–0·3μ. "Attempts to transplant the tumour directly from the mouse to either the rat or the guinea pig were uniformly unsuccessful." When the chambers were inserted intraperitoneally in rats or guinea pigs the growth of the mouse cancer cells was at least as prolific as in mice. "It was found that growth of the tumour in the rats and guinea pigs was as good as or better than it had been in mice, and the day-by-day growth characteristics were studied. It would appear that the tumour-host hostility evident on direct inoculation was dependent on cell-to-cell contact between tumour cells and the host."

Studies in geographical pathology come from the University College of North Wales ("Cancer Incidence in Relation to Trace Elements in Soil and Plants"), Makerere College, Uganda ("Cancer in African Children") and the University of Bristol.

Statistical data from the Bristol Tumour Registry show that under the age of 40 the English incidence of bone sarcoma is similar to Norwegian figures. After that age the tumour is much more common in south-west England, due largely but not entirely to the frequency of Paget's disease of bone in the English population, but not in the Norwegian population. Except in those subject to Paget's disease the tumour has a monomodal age incidence curve, the English incidence showing a typical bimodal curve.

Paget's disease (osteitis deformans), probably the commonest non-traumatic disease of bone seen in an orthopædic department, was described in some detail in 1876 by Sir James Paget. It has been described in animals, too, and is an etiological feature of canine osteogenic sarcoma, where it is much more common in some breeds than in others. The author of this study is clearly aware of the need to combine a knowledge of geographical pathology with genetics, comparative pathology and basic clinical observation in the elucidation of the most fundamental aspect of any disease —its natural history.

A report on a clinico-pathological investigation of cancer of the cervix uteri concludes that: (1) beyond a certain dosage (irradiation) range the physical modalities of irradiation do not significantly alter the cure-rate for cancer of the cervix; (2) the clinical extent of the disease and such quantitative biological characters as Broder's grade and size of tumour foci have a significant influence on the five-year survival-rate; (3) among the qualitative biological characters the histological type of the tumour and its ability to respond initially with an increase in differentiation profoundly affect the cure-rate; (4) systemic factors, of yet unknown character, can control the growth of persisting cancers for long periods.

The same, or similar, methods of treatment, unmodified in essentials for perhaps 20 years or more, are in use in hospitals throughout Britain, and naturally their reports read much the same. At present the clinician subscribes to earlier diagnosis as well as better surgery, irradiation or chemotherapy as one of the principal means of improving results. Not in all cases is this meaningful; the patient with an enlarged lymph node due to lymphosarcoma has

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both the earliest and the established pattern of the disease; the patient with a skin blemish can watch, if he wishes, the growth of a curable cutaneous cancer. Carcinoma of the lung is different from both; it produces symptoms (that is, something of which the patient complains) as a by-product of its naturally hidden position and will produce them when quite small should it simultaneously involve a blood vessel and a small peripheral bronchus, when blood-stained sputum may be expectorated, but commonly is measured in centimetres and produces the first symptoms due to remote spread. The size of a tumour, its duration or its clinical accessibility or visibility are not in themselves important in prognosis. The overriding factor is our knowledge based on experience of the natural history of each type of tumour. For example, the prognosis in the case of squamous cell carcinoma depends on which organ it primarily involves, and extrapolation from one species to another must be done with extreme caution. Nevertheless, any basic studies of that neglected field—animal pathology—are most welcome. A complete understanding of tumour behaviour must include such knowledge, hence the work of Silver and Cater on the treatment of spontaneous tumours in animals by radiotherapy or by chemotherapeutic agents offers a little hope that research workers have not forgotten the value of comparative investigations.

Prof. Bullough's group at Birkbeck College continue work on the diurnal mitotic rhythm of normal mouse epidermis, and conclude that it is due to the hour-by-hour variations in the ability of prepared cells to enter division and not to hour-by-hour variations in the numbers of cells preparing to divide; that the ability of cells to enter division depends on variations in the secretion-rate of adrenalin; and that these variations in turn depend on a degree of stress felt by the animal, stress being higher when a mouse is awake than when it is asleep. On this fascinating work one could build, with little imagination, a hypothesis accounting for human cancer as, in part, a psychological disorder. (This has been attempted in the past with no convincing success, but a careful psychosomatic approach to human cancer is worth while.)

With the chemotherapeutic agents at present available, one of the practical problems is that of delivering a dose of a drug which will result in the death of tumour cells, but which is not lethal to the patient; drugs with a greater specificity towards tumours are being developed while, at the same time, techniques using existing drugs aim at better localization. Where the tumour is in a limb, this becomes a fairly simple matter of perfusion; where the growth is widely disseminated, the urgent problem is to preserve a bone marrow which can regenerate after severe depression or even total death of bone marrow following administration of chemotherapeutic agents. Techniques vary from using living fœtal marrow from a fœtal tissue bank or the storage of the patient's own aspirated marrow for later re-injection, to an ingenious technique reported by Starr in New South Wales, where the patient's aspirated marrow is injected into a drill-hole in the tibia after a tourniquet is applied, only to be released after an otherwise lethal intravenous dose of cytotoxic drug has become fixed or eliminated, in 1–3 hr.

At Makerere College, Uganda, animal tumours are investigated by exfoliative cytology, many tumour cells being studied to greater advantage when flattened on glass slides than in paraffin sections. In the case of the transmissible (venereal) tumour of the dog it has been found that the round cells infiltrating the lesions are plasma cells, frequently binucleate with a 'mirror image' pattern. In enzootic hæmaturia of cattle (a disease characterized by progression of papilloma of the bladder to carcinoma) investigations have confirmed the findings of some Turkish pathologists, and support a viral origin of the condition. These cytological observations show that the bovine urinary bladder has secretory function. Well-known virus diseases of animals—canine distemper and infectious pneumonitis of cats—are now being investigated by this rapid method of study.

As for many years past, the report provides plenty of evidence of the widespread use of physical techniques involving radiation and radioisotopes; this year there is evidence of the rapid extension of diagnostic and research uses of the latter in remote parts of the world. But there is little which is sufficiently novel to require mention. Hospital physicists, perennially suffering from erratic radiation background, will be interested to know that, at the Royal Cancer Hospital, an attempt is being made to build a low-background room on a small outlay of money. Chalk in paper bags, 2 ft. thick, is being used for this, the inner surface of the room being lined with ¼-in. aged lead. Another development which looks like being of practical importance is taking place at the Middlesex Hospital, where the radiation-induced destruction of the fluorescence of quinine sulphate is being investigated as a method of measuring γ- and X-ray dosage. The results suggest that doses of 10 rads or even less can be estimated with good accuracy; it will be interesting to hear further of this work.

Among radiotherapeutic developments note should be taken of the Royal Cancer Hospital's use of solid sources which have been made radioactive by neutron bombardment. These include a Souttar's tube, for treatment of the œsophagus, made of silver-plated nickel wire containing a core of gold; and two laryngectomy tube applicators of copper-nickel alloy, giving, after activation, a dose-rate of the order of 200 rads/hr. The Department of Radiotherapeutics at Cambridge has continued its efforts, noted here last year, to use the selective uptake of tritiated 'Synkavit' in cancer as a therapeutic measure. Information is given on methods of administration, dosage, and means for increasing selective concentration. Information is also given on the degree of selective uptake in various types of tumour-tissue as compared with bone-marrow. Investigations, subject to the usual limitations, have been made on patients and the results are so far inconclusive. On the other hand, parallel investigations on animals which are also reported look promising. A similar line of investigation is reported from the Sheffield Regional Radiotherapy Centre, where the selective uptake of radioactive zinc-labelled hæmatoporphyrin has been investigated with encouraging results; however, no details are given.

The Leeds centre is making a new approach to the study of bone mineralization. Attempts are being made to relate the transmission through bone of radiations of markedly different quality to the quantity of calcified bone lying in the path of the beam. Thulium-170 and cæsium-137 have been used in this work which, if successful, will make it possible to study bone mineralization by *in vivo* methods.

D. G. Arnott
I. Hueger
A. L. Levene

EVOLUTION OF REGENERATION, AND ITS POSSIBLE BEARING ON PHILOSOPHY

NEEDHAM[1] has recently criticized the view of Morgan and others that the distribution of regenerative capacities is not closely correlated with their adaptive value. This criticism, if accepted, can be used to answer one objection to the Neo-Darwinian interpretation of regeneration and its evolution. Other problems remain. Regeneration, when adaptive, is a secondary adaptation; it is the adaptation of an adaptive embryonic sequence to the special conditions under which regeneration occurs, the relation between the primary and secondary adaptation being one of likeness in the final developmental product, and often of unlikeness in the processes of development. A spectacular instance is the regeneration of the urodele lens. In cases such as this, it may fairly be assumed that regenerative processes are adaptive only if they restore a close copy of the part lost. This imposes a stringent condition for the selection of regenerative mutants, if the capacity for regeneration has evolved in this way.

In the present state of ignorance about the genetic basis of regeneration, the following alternative assumptions appear open to orthodox evolutionists. The first alternative assumes that different or partly different groups of genes are active in regeneration and embryonic development, each set embodying different instructions for, for example, lens-making. On the other assumption, the same genes are involved in both cases, causing different developmental processes in different circumstances.

The first alternative implies a highly improbable convergence in the evolution of embryonic and regenerative development, with close correspondence, at different evolutionary stages, between the end-products of independently varying gene assemblies. Such an ontogenetic convergence, maintained throughout an evolutionary series, would be less comprehensible, on the assumption of random genetic change, than convergent evolution between different species, where the resemblances are less exact.

On the alternative assumption, the evolution of regeneration may be ascribed to selection for genetic changes which facilitate double-track development by the same genetic determinants. Such genetic changes are required: (1) to leave unchanged former developmental tracks, at least with respect to their end-product; (2) to initiate new tracks, the usefulness of which depends on their leading to the same end-state as the old tracks. The same paradox arises here as on the assumption of independent genetic controls for embryonic and regenerative development: the paradox of ascribing the replication of identical structures, through different developmental processes, throughout an evolutionary sequence, to random genetic changes which have been selected. It is legitimate to doubt whether so exact a coincidence of results could have come about in this way. There seems to be no evidence for the occurrence of equifinal regenerative mutations, having the developmental effects outlined above.

Equifinality or end-invariance, attained through variable precurrent events, is a pervasive property of life and the products of life[2], from the cellular to the social and technological grades of organization. Its elucidation would probably be of philosophical significance, as offering the lure of the long-awaited solution of the mind/body problem, and of a general concept of organic causation connecting final with efficient causes. The split between these may be linked with the dualism of spectator and participant. Activities which, to a spectator, appear determined by past causes, to their participants, appear aimed at future ends. While in atomic physics it has become necessary to emphasize the impact of the observer on the observed, in evolutionary biology it is necessary to note the impact, mediated by a common descent, of the processes studied on their students' ways of thinking about them. Awareness of this impact implies an almost existentialist sense of personal involvement in evolutionary processes, out of which has somehow surprisingly sprung the human capacity for concern over evolution, past and future. What may be called a detached spectator's view of evolution, the *post factum* assessment of evolution as determined by efficient causes, makes a coherent and comprehensive theory of evolution impossible, so long as the relation between these efficient causes and the development of the capacity for future-directed action remains a mystery. (Darwin's famous personification of natural selection, as the never off-duty scrutineer of variation, vividly reflects the view that the course of evolution has been determined by factors in principle observable by a sufficiently acute and unremitting onlooker. Another symptom of the spectator's point of view, in Darwin and some modern writers on evolution, is the disproportionate emphasis on external adaptations to specific features of the environment, and the comparative neglect of the integrative and regulative capacities of the organism in development and self-maintenance.)

All historical studies of past life are liable to be conducted from a spectator's point of view, including the study of human history. One reason for this is that the working back from present to past, characteristic of all historical inference, reverses the natural order of events, and obstructs their evaluation from past to future, from the participants' point of view.

From our present grasp of the mechanisms of evolution, we can no more derive the evolution of purpose than from our present understanding of cerebral mechanisms we can derive either the 'inner' or 'outer' aspects of behaviour. Consequently, claims that Neo-Darwinism provides a coherent synthesis of all the known relevant facts are baseless. The interest and challenge of equifinality lie in its hint that we do not have to resign ourselves to this incoherence, and that the struggle for a unitary conception of unconscious organic processes and mental processes, within an evolutionary framework, may not be vain. Possibly these processes are not merely analogous, with respect to equifinality, but even homologous, in the sense of having a common evolutionary origin. There seems no compelling reason why the search for homologues of mind should be restricted to the field of behaviour. As Sinnott[3] and others have pointed out, the dividing

line between development and behaviour is a fine one. If behaviour is not fully describable in spectator-language, the same may be true for development. (This does not imply that developmental processes may be conscious. We learn from self-consciousness that some vital functions are directed at future ends.

It does not follow that all future-directed processes are conscious. Consciousness may reveal one facet of organic functioning without constituting its essence.) This possibility cannot be excluded, so long as the problem of development, as at present conceived—how the 'genetic code' is 'made flesh' and conditions the psycho-physical attributes of the adult—remains unsolved. In principle, the attempt to define ontogenetic precursors or rudiments of mind seems not less justified that the corresponding attempt in phylogeny. (Not on the ground that ontogeny repeats phylogeny, but on the ground that we should seek to connect later states of a system with earlier ones.) A conceptual bridge is yet to be built between the human zygote, considered as a biochemical system, and the purposiveness of the adult man, if the latter is to be explained partly as a consequence of the former. It is plausible to look for this bridge in the intervening processes of development, and especially in the interpretation of the 'anticipatory'[4] appearance of development, the pre-functional elaboration of parts destined to become an integrated system of functional organs in the adult. No theory of development can be deemed satisfying which does not offer an explanation of this progressive realization of functions, just as no theory of the neuro-physiology of behaviour is satisfying which does not explain how the progressive realization of a future end-state is possible. (In neither case can selection theory provide a substitute for an analysis of the concurrent causes of this central feature of development and behaviour.

That there has been selection for mechanisms which expedite future survival does not tell us what these mechanisms are. Disregard of this led to the nineteenth-century error of substituting speculations about phylogenies for analysis of ontogenies. Development theory has been retarded first by being viewed exclusively through Darwinian spectacles, and more recently through Mendelian ones. Mendelism abstracted from the forward thrust of developmental processes, and concentrated on correlating starting-points with end-points, parental phenotypes with filial phenotypes. Necessarily, the concept of the gene arrived at by these methods is inadequate as a basis for development theory. This abstractive tendency of genetics is re-inforced by modern concentration on the genetics of micro-organisms, with their relatively simple ontogenies. It is possible in the future that development theory will influence conceptions of genetics and evolution as deeply as it has hitherto come under their influence.) The temporal organization of vital processes, which makes meaningless any analysis of the organism-at-an-instant, presents similar patterns and problems for all the life sciences. Information theory has made familiar the notion that organisms store up information from the past, both in their brains and their germ-cells. Possibly a similar generalization will prove fruitful with respect to the forward direction of organic processes, which often proceed as though organisms possessed information about the future, and may produce an adaptive end-result even in circumstances different from those encountered in the (phylogenetic) past—as when a normal adult develops from the fusion of two amphibian eggs. Unless some generalized concept can be made to cover all instances of future-directed functioning, it is hard to see how the reference to the future involved in conscious anticipation can be made intelligible in relation to its ontogenetic and phylogenetic history, and one possible ideal of theoretical biology will have to be abandoned.

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Dr. Spilsbury renders a general service in bridging the gulf between philosophy and biology, and a special service to biology in focusing attention on regeneration as a critical test case of the ability of the Darwinian theory to explain the mode of evolution. His suggestion that the genetic determination of regenesis (the process of regeneration) may be independent of that of normal ontogenesis also must interest biologists. Can we be sure that natural selection is a factor powerful enough to establish perfect convergence between the paths of these two morphogenetic processes, and also to maintain the perfection of the convergence throughout a long evolutionary series of changes in the final, adult form? As Spilsbury has further pointed out in correspondence, selection in favour of regenerative ability seems to be much weaker than that in favour of normal ontogenesis since, while the latter is inevitably demanded, the former is only possibly evoked in each individual life. Normal development is a *sine qua non* for propagation by the individual whereas often regeneration is called for only late in the reproductive phase of life. Consequently even if natural selection provides an adequate explanation of the evolution of normal ontogenesis, it may not be adequate to explain the perfect convergence by regenesis. By the same token, however, if it should prove a sufficient explanation of the latter then we need have little doubt that it can explain the evolution of ontogenesis and of biological adaptations in general.

An exact mathematical approach, by Fisher and Haldane in particular, has emphasized how small an advantage may have selective value for the individual, and survival value for the species. Successful regeneration, even if called for in only a small percentage of individuals, provided it enables them to make a further small contribution to the size of the next generation may make just the difference between an assured survival and an inevitable extinction for the species. This is true even on the assumption that regenerative power is equal in all the individuals of a species, but there is also likely to be selection differentially in favour of individuals combining a high regenerative power with other advantageous characteristics. Moreover, regeneration is not so rare in the field[1] as implied above and this is further supported by a recent census on populations of three species of *Planaria*. Between 25 and 50 per cent of the individuals of the different species were in process of regeneration at that moment, so that each individual is likely to be challenged several times during its life. Selection in favour of regenerative ability therefore is stronger than appears at first sight.

The perfection of the convergence between ontogenesis and regenesis should not be overstressed. It is usually extremely good, but mistakes sometimes

occur and the lizard's tail habitually regenerates rather a makeshift for the original structure. This may adequately serve its biological purpose, however, and the whole variety in degree of convergence is consistent with a natural selection basis.

It must also be remembered that the power of regeneration is as ancient as that of ontogenesis itself, that asexual reproduction and other morphogenetic processes grade into that of regenesis[2], and that ontogenesis and regenesis have evolved together, step by step, throughout their long history. It would perhaps be surprising to find anything but quite close convergence between them. It also seems probable that in general the same genes control both. In arthropods abnormalities such as the regeneration of a leg in place of an antenna are paralleled by similar abnormalities of ontogenesis, and these are known to be determined in typical Mendelian fashion. Regeneration probably can be regarded as just a special case of what Wigglesworth[3] has called 'developmental polymorphism'; the insect embryo produces a first set of legs and other organs, and then a new, imaginal set is produced at metamorphosis. There are also other pieces of evidence that ontogenesis and regenesis are components of a common mechanism[2], and we can scarcely regard the convergence between them as special evidence in favour of final causation. This does not affect the possibility that they, and all biological phenomena, show more general evidence of the operation of final causes; but most biologists believe that natural selection could have produced the apparent purposefulness in the many interesting cases discussed by E. S. Russell and others. Among these, internal homœostatic mechanisms do figure, of course, if not as frequently as external anatomical features.

Final causation as usually understood is perhaps a problem purely for the philosopher, since it is scarcely amenable to the scientific approach. At the same time biologists must be as much concerned as philosophers in the problem of reconciling their respective approaches to the acquisition of knowledge. This problem stems largely from the differences between the axiomatic premises of the two approaches and, so long as these remain, it is not reasonable to expect any ultimate integration of their views. By axiomatic law final causation, as usually understood, is ruled out of the scientific court and no amount of subsequent pleading can bring it in again. It may be a reality, but it cannot be tested experimentally.

Some biologists might regard natural selection as somewhat in the position of a final cause[2] in the sense that it has the appearance of acting in the manner of a *deus ex machina* on the fundamental processes governed by efficient causes. It has the virtue of being a cause which can be investigated by observation and experiment. For this very reason it is not a final cause in the usual sense but may prove to be all we need to seek. It has been pointed out[4] that the conception of natural selection is just another way of saying that at every time and place only the viable systems survive: few would object to the view that the final cause of life is its viability. Survival of the viable, and extinction of all other, systems may be generalized into the principle that what actually occurs in each spatio-temporal context is the most probable event in that context. The viable automatically behave as though directed towards the goal of survival. In the behaviour of the higher animals this has become very purposeful in appearance. The anticipatory character of ethological responses and of ontogenesis certainly appears purposive to an observer but it should be remembered that these activities are largely recapitulatory of past experiences, of the individual and the species respectively, and are not purposive aims at entirely novel objectives.

The 'most probable' conception of final causation, originating entirely from within a biological outlook, could ultimately provide a coherent and comprehensive account of evolution which might meet the requirements of philosophers. At the same time it discourages the idea that there is necessarily a sharp psychophysical dualism in the phenomenon of life. Spilsbury believes that this dualism also corresponds to one between subjective and objective experience, but it is perhaps debatable if our subjective experience is anything beyond an objective study of ourselves.

Dr. Spilsbury raises a number of minor issues which many biologists might wish to take up, but it would be wrong to obscure his main thesis by pursuing them here. There are also one or two puzzling passages, such as the apparent contradiction between the two properties demanded of any prospective change in the genetic control of regeneration, and some unguarded phrases such as "organic causation", "expedite future survival" and " . . . 'inner' and 'outer' aspects of behaviour".

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COMPARATIVE EFFECTS OF WET AND DRY FEEDING ON THE UTILIZATION OF PROTEIN BY CALVES

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IT is generally accepted that when liquid milk is fed to young calves it by-passes the rumen and reticulum, by means of the œsophageal groove[1], and enters directly into the abomasum. This permits the food to undergo monogastric digestion. The recent trend towards the early weaning of calves by a system involving dry feeding of concentrate meals is associated with the early development of a functional rumen. However, fermentation in the rumen is a relatively inefficient process, which penalizes the

Table 1. PERCENTAGE COMPOSITION OF THE DIETS

Ingredients	Diet *X*	Diet *Y*
Hay (crude protein, 6·99 per cent of dry matter; crude fibre, 35·5 per cent of dry matter)	25	25
Spray-dried, separated-milk powder	20	—
Fatted milk powder*	—	40
Rolled barley	30	7
Barley meal	10	10
White fishmeal	15	18

* The fatted milk powder was prepared by the homogenization of crude red palm oil with liquid separated-milk, followed by spray drying in a commercial plant to produce a powder containing 50 per cent of fat.

utilization of those carbohydrates which are capable of being well assimilated by monogastric digestion. It seems likely that even when calves are receiving hay, and behaving as functional ruminants, the feeding of the concentrate part of their diet as a gruel enables this food to bypass the rumen. If the carbohydrates are then more efficiently utilized than when fed dry this should increase the available energy of the diet, and thereby improve nitrogen retention[3]. It was therefore decided to examine the comparative effects of wet and dry feeding on the nitrogen balance of calves.

Four ruminating Ayrshire bull calves, approximately 14 weeks old and housed in metabolism crates, were used for the investigation. Two diets were made up as shown in Table 1, the hay being kept separate from the other components. Chlortetracycline (17 mgm. per lb. of diet) and supplements of trace minerals and vitamins A, D_3, E and the B complex were included. Each diet was allocated to two calves. In all the balance periods (periods 7, 8 and 9) the daily allowance of meal for each calf (1,050 gm.) was given in two equal feeds, at 9 a.m. and 5 p.m. The daily allowance of chopped hay (350 gm.) was given immediately after the morning feed. For the first and last parts of the experiment (periods 7 and 9), the 525 gm. of meal for each feed was mixed with two litres of warm water and bucket-fed immediately. During period 8, the meal was fed dry, followed by two litres of warm water per calf. Each balance period of eight days was preceded by a preliminary period of six days. The collection and analysis of fæces and urine were carried out as previously described[3], except that fæcal nitrogen determinations were made on composite wet samples at the end of each period.

The effects of dry and wet feeding on the mode of absorption of the carbohydrates were studied at the end of periods 8 and 9 by measuring the changes in reducing sugars of the blood following a normal meal, and also one containing in addition 200 gm. glucose. The reducing sugars were determined by King's method[4] on samples of blood taken at 0, 1½, 3, 6 and 8 hr. after feeding.

It is evident from the results in Table 2 that the retention of nitrogen by each calf was markedly lower with dry feeding than with wet feeding. Since dry feeding was associated with a somewhat greater digestibility of the crude protein, the differences in nitrogen retention were due to differences in the extent to which absorbed nitrogen was retained. It should also be noted that the efficiency of nitrogen retention was much higher on diet *Y* (the high-fat diet) than on diet *X*, with each method of feeding, suggesting that lack of available dietary energy was at all times an important factor in limiting the retention of nitrogen.

From the changes in reducing sugars of the blood 1½ hr. after feeding the respective meals without added glucose (Table 2), it is evident that all four calves showed appreciable rises following wet feeding compared with much smaller changes after dry feeding. This difference in response to wet and dry feeding supports the view that wet feeding enables a considerable proportion of the food to pass directly into the abomasum, whereas dry feeding is associated with entry of the food into the rumen, with subsequent fermentation. Lactose has previously been shown to be capable of producing an appreciable rise in reducing sugars of the blood[5], and since the single feed of each diet would supply an estimated 70 gm. of lactose, some of the response must have come from this source.

Further evidence is provided by the results obtained when 200 gm. of glucose were added to the food. Calves 1, 2 and 3 showed little or no response to the added glucose with dry feeding, but very marked responses with wet feeding. In the case of calf 4, although there was an appreciable rise in blood glucose following dry feeding, this was greatly increased with wet feeding.

It is of interest to note the greater rises in blood sugar on the high-fat diet since this has also been observed in studies of human nutrition[6].

Table 2. COMPOSITION AND DIGESTIBILITY OF DIETS, NITROGEN BALANCE, AND BLOOD REDUCING SUGARS

Composition of diets (dry matter basis)	Diet *X*						Diet *Y*					
Crude protein (per cent)	25·7						24·3					
Ether-extractable material (per cent)	2·49						24·0					
	Calf 1			Calf 2			Calf 3			Calf 4		
Period No.	7	8	9	7	8	9	7	8	9	7	8	9
Mean live-weight of calf* (lb.)	158	167	176	149	161	167	160	179	185	159	174	188
Method of feeding meal	Wet	Dry	Wet	Wet	Dry	Wet	Wet	Dry	Wet	Wet	Dry	Wet
Apparent digestibility of diets												
Dry matter (per cent)	73·0	79·1	77·2	75·6	81·7	78·9	78·6	77·3	75·0	77·6	79·3	79·2
Crude protein (per cent)	75·8	83·0	79·9	82·5	85·5	81·7	81·6	82·7	80·9	80·3	84·0	80·2
Nitrogen balance												
Intake (gm./day)	51·7	51·7	51·7	51·7	51·7	51·7	50·0	50·0	50·0	50·0	50·0	50·0
Retention (gm./day)	13·5	6·65	10·1	14·9	10·2	13·4	23·7	14·4	21·3	25·5	17·2	24·3
Retention (per cent of intake)	26·1	12·9	19·5	28·8	19·7	25·9	47·4	28·8	42·6	51·0	34·4	48·6
Blood reducing sugars												
Change at 1¼ hr. after feeding (mgm./100 ml.)												
Meal only		+2	+27		+11	+21		−4	+44		+7	+53
Meal + 200 gm. glucose		−12	+38		−2	+30		+6	+85		+44	+143

* Mean of initial and final weight for each period.

It seems that the feeding of the meal part of each of these diets in the form of a gruel enabled a large proportion of it, if not all, to by-pass the rumen. This was associated with markedly better utilization of dietary protein, presumably brought about mainly by a more efficient use of dietary energy.

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INFLUENCE OF AGE OF MICE ON THE RECOVERY FROM EXPERIMENTAL SENDAI VIRUS INFECTION

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THE view is now prevalent that Sendai virus[1] (*Myxovirus parainfluenzae* 1)[2] persists in laboratory mice mainly in the Far East. Attempts to produce a persistent infection in mice, carried out by C. H. Andrewes and me[3], were unsuccessful. Intranasal infection occasionally caused lethal pneumonia, but among animals which recovered it was observed that adult mice eliminated the virus much earlier than the suckling ones. This indicated that the recovery process in very young mice might be handicapped.

In order to study this further 4 weeks old mice were inoculated intranasally with 0·05 ml. and suckling mice infected during the 1st day of life with 0·01 ml. of allantoic fluid containing 100 EID_{50}/ml. of Sendai virus. Five adult mice along with 5 sucklings were killed 4 and 6 days and daily from 8 to 15 days after infection. The presence of virus was checked by sub-inoculation of the lung extracts from individual mice into 11-day-old chick embryos. The results of this experiment are shown in Table 1. In adult mice,

Table 1. Persistence of Virus in Adult and Suckling Mice at Various Times after Infection

Numerator: number of mouse lungs yielding virus. Denominator: number of mouse lungs tested

Mice	Days after infection									
	4	6	8	9	10	11	12	13	14	15
Adult	5/5	5/5	4/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Suckling	5/5	5/5	5/5	5/5	5/5	2/5	1/5	4/5	1/5	0/5

virus was no longer recovered after the 8th day of infection, whereas in suckling mice virus was detectable up to 14 days, the titres being high up to the 9th day after infection (ID_{50} tests in pieces of chick chorioallantoic membrane[4]). In the same experiment sera of adult mice were tested at various times after infection for the presence of hæmagglutination inhibition antibodies. No antibody was found. Lung extracts of infected adult mice contained small amounts of viral antibody as measured by the hæmagglutination inhibition test from the 8th day after infection (Fig. 1). No antibodies were found in lung extracts of the suckling mice up to the 15th day after infection. While one cannot exclude the possibility that local hæmagglutination inhibition antibodies might have influenced the elimination of virus in adult mice, it is difficult to support this explanation in the case of suckling mice which eliminated virus by the 15th day after infection despite the complete lack of any detectable hæmagglutination inhibition antibody in their lungs.

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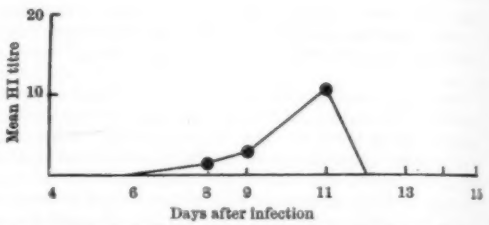

Fig. 1. Hæmagglutination inhibition (HI) antibodies in lung extracts of adult mice at various times after infection. Mean titres of five lungs individually tested

There are reports which indicate that an important role in recovery from primary viral infections may be played by interferon[5–9]. In this connexion it is of interest that recovery from viral infection can occur in the absence of any antibody formation, for example, in the chick embryo, or in the presence of only traces of antibody, for example, in patients with hypogammaglobulinæmia[9].

Experiments were therefore set up to compare interferon production in experimentally infected adult and suckling mice. Three animals of each group were killed 2, 4, 6 and 8 days after infection.

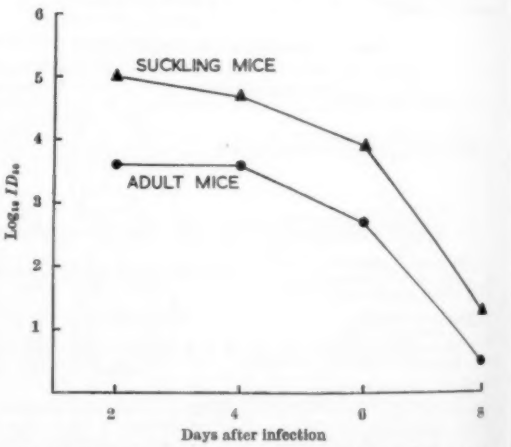

Fig. 2. Virus titres in lung extracts of adult and suckling mice at various times after infection. Pools of three lungs tested at day indicated, mean titres of four experiments

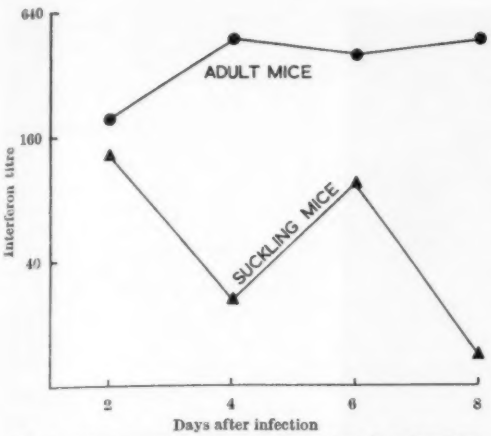

Fig. 3. Interferon titres in lung extracts of adult and suckling mice at various times after infection. Pools of three lungs tested at day indicated, mean titres of three experiments. Titres shown as the reciprocal of the dilution of lung extract causing 50 per cent reduction in the virus plaque counts

The lungs taken at each time-interval were pooled and extracts prepared. The amount of saline used for the extracts was adjusted according to the weight of the lungs. The material was tested for the amount of virus present (ID_{50} titrated in chick embryos) and interferon content (plaque reduction test in mouse embryo fibroblast monolayers infected with approx. 100 plaque-forming units of encephalomyocarditis virus[5]). Four such experiments were carried out, and the combined results are presented in Figs. 2 and 3. As can be seen from the graphs, the virus titres were higher in suckling mice, and interferon content lower than in the infected adults. No significant differences in interferon content were seen at the early stage of infection but differences became evident towards the end of the infectious process—during recovery.

As was indicated earlier, the speed of virus elimination as an indicator of the recovery process in adult mice might have been influenced by locally produced antibody. In the lungs of the infected suckling mice no antibodies were found, and there is suggestive evidence from the experiments described here that the recovery process was influenced by the amount of interferon produced. The lower content of interferon in the lungs of the infected suckling mice could be responsible for both the higher virus titres during the course of infection and the longer persistence of virus.

Differences in the course of both naturally and experimentally induced viral infections in young as compared with adult animals have been repeatedly described in the past and with few exceptions[10] they indicated that younger animals were more susceptible to infection with many different viruses[11–22].

Acquired resistance of growing animals to certain neurotropic viruses in the absence of humoral antibodies or previous exposure to these viruses was described as early as in 1936 by P. K. Olitsky *et al.*[11]. The factors which might have influenced the refractory state of adult animals were considered obscure.

Very young mice showed a higher susceptibility to rabies virus infection than adult mice, but only when fixed virus was used[19]. In this connexion it is worth mentioning a recent finding that attenuated virus is a better producer of interferon than virulent virus[23].

It has been found that during maturation of the embryo there is a steady increase in the sensitivity of the cells to interferon and in their ability to produce interferon[6]. The present results suggest that this process may continue during post-embryonic life and that this may be a factor governing the response to virus infection in young animals.

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CLOSELY RELATED ANTIGENS IN HUMAN PLACENTA AND KIDNEY

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ONE of the many theories of the etiology of toxæmias of pregnancy maintains that maternal antibodies formed against placental antigens may damage maternal glomeruli. In order to support this hypothesis, it would be desirable to demonstrate that human placenta and human glomerular basement membrane contain closely related antigens; and secondly, that the placenta has a mechanism by which these closely related placental antigens might vary sufficiently to 'appear' foreign to the mother so as to provide an antigenic stimulus. The antibodies formed against this antigenic stimulus could be expected to collect in the human glomerular basement membrane and initiate glomerular damage. This hypothesis is based on the premise that in order for antibodies to damage tissues, they would first have to be present in the affected tissues. Such antibodies could properly be called autoantibodies and this mechanism an autoimmune mechanism.

Seegal reported that the rat[1] and dog[2] placenta and kidney contain nephrotoxic antigens in common. Cruickshank and Hill[3] reported fluorescein-labelled

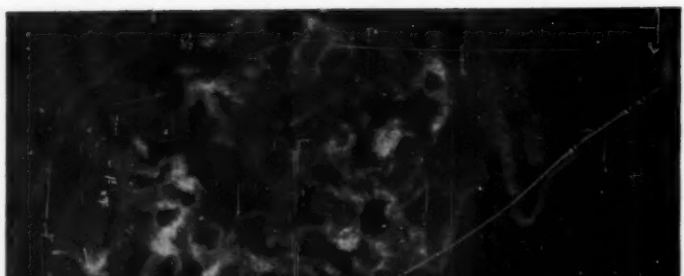

Fig. 1. Fluorescent photomicrograph of a human kidney stained *in vitro* with sheep anti-human placenta fluorescein conjugates. The basement membranes of glomeruli, Bowman's capsule and tubules show specific apple-green fluorescence which appears white in the photograph. Note the tubule opening into Bowman's space. Cellular structures do not stain. Identical results were obtained with sheep anti-human glomerular basement membrane fluorescein conjugates. (× *c.* 525)

rabbit anti-rat glomeruli serum stained connective tissue structures in various rat organs and was nephrotoxic for rats. Evidently nephrotoxic antibodies are part of the localizing antibodies. Since direct bioassay is not possible in man, the demonstration of heterologous antibodies to human placenta which collect in human glomeruli would prove that human placenta and glomeruli share closely related antigens. Such localizing antibodies might be nephrotoxic.

Since little is known about the relationship of antigens in human placenta and kidney, this investigation was undertaken to determine if human placental antigens were present in human kidney and where such antigens were located, using the immunofluorescent technique of Coons[4].

Human glomerular basement membrane was prepared as previously described[5]. The membrane was suspended in isotonic saline to a concentration of about 80 mgm. per ml. A 1 : 1 water-in-oil emulsion was made with Freund's adjuvant consisting of 85 ml. 'Bayol *F*', 15 ml. 'Arlacel *A*' and 200 mgm. *Mycobacterium butyricum* (Difco).

A human placenta was obtained shortly after birth, freed from membranes and washed grossly free of blood. Minced placenta and isotonic saline were mixed in a Waring blender for several minutes and then incorporated into Freund's adjuvant. Additional saline was added until the final concentration of placenta in the emulsion was about 1 gm./6 ml.

About 6 c.c. of the human glomerular basement membrane emulsion and 30 c.c. of the placental emulsion were injected into individual sheep by intramuscular, intradermal and subcutaneous routes every 2 weeks. Each sheep was bled to death one week after the fifth injection. The sera were removed and stored in the deep freeze (− 15° C.) until needed.

The globulin fractions were separated from the sera by half-saturation with ammonium sulphate or the cold alcohol fractionation method of Deutsch[6]. The γ-globulin was conjugated to fluorescein isothiocyanate according to Riggs's method[7].

Human kidney tissues were obtained soon after autopsy or from surgical specimens. Human placentas were obtained immediately after birth. Portions of tissue were frozen in isopentane cooled by a mixture of dry ice and acetone, and sections 4 microns thick were cut in a cryostat. The fluorescein - conjugated antisera were passed through a 'Dowex' resin column and then absorbed with 150 mgm. of acetone-dried mouse liver powder per c.c. of conjugated serum. In addition, 1 part of antiserum was absorbed with 2 parts of oxylated whole human blood.

The absorbed antisera were then used directly to stain the tissue sections and careful controls were used as described by Coons[4]. The slides were examined with a Leitz microscope fluorescence unit and permanent photographic records were made.

Fluorescein-labelled sheep antibodies to human glomerular basement membrane or human placenta stained identical connective tissue structures in the kidney. These structures may be defined as the basement membranes of glomeruli, tubules, Bowman's capsules and intertubular capillaries. Certain extracellular structures in the media and adventitia of arteries were also stained. The stained structures in the media of arteries might correspond to the basement membranes of smooth muscle cells according to Gersh[8]. The structures in the adventitia of arteries might represent irregularly condensed ground substance.

Fluorescein-labelled sheep antibodies to human placenta and human glomerular basement membrane stained the placenta in similar manner. Specific staining was diffusely present throughout the entire connective tissue core of the villus with heavy concentration in blood vessel walls and in the subsyncytial cell layer.

Cellular structures in the kidney and placenta did not show specific staining. None of the control sections showed the specific apple-green fluorescence. An interesting incidental finding was the observation that autofluorescent internal and external laminæ were not seen in placental blood vessels encountered even though some were of large size.

The results of these preliminary experiments indicate clearly that human placenta and human glomerular basement membrane share a closely related antigen or group of antigens. Further, that the placenta contains an antigen or group of antigens which is present in various connective tissue structures of the kidney.

The chemical nature of the antigen (or antigens) is unknown. The areas that stain most intensely in the placenta and kidney with fluorescein-conjugates are also periodic acid–Schiff positive. Mature collagen is reported not to stain in rats[3] and man[2], using anti-glomeruli fluorescent conjugates. It would seem unlikely that collagen fibrils are the antigen involved in the present investigation.

In general, nephrotoxic sera have been shown to stain many connective tissue structures of many

organs *in vitro*[8] but to be largely confined to glomerular basement membranes *in vivo*[10].

Since anti-rat and anti-dog placenta sera have been shown to be nephrotoxic, and nephrotoxic sera are always localized on the glomerular basement membranes *in vivo* and *in vitro*, it would appear reasonable to speculate that anti-human placenta sera which are localized on human glomerular basement membrane *in vitro* might also contain glomerular-damaging antibodies among the localizing antibodies. Certainly absence of localization on the human glomerular basement membrane by anti-human placenta sera would be substantial evidence against glomerular-damaging antibodies being present.

Recently, Dixon[11] has shown that repeated intravenous injections of foreign protein produces glomerular damage in rabbits by means of antigen–antibody complexes. These complexes become localized in and damage glomeruli without any immunological specificity for kidney antigen. This alternative method of damaging glomeruli would have to be considered in the etiology of toxæmias of pregnancy because placental antigens might continually leak into the maternal circulation and form antigen–antibody complexes which become localized in glomeruli for non-immunological reasons and damage them.

Although the basement membranes in many organs may contain antigens in common with the maternal human glomerular basement membrane, the placenta is unique during pregnancy. The placenta is the only organ in the body which has the capacity to vary its antigenic structures by paternal contribution to its composition. This variation may be sufficient to cause some of the antigens to appear 'foreign' to the mother yet sufficiently related to cause the antibodies produced to cross-react with closely related antigens in the human glomerular basement membrane and produce glomerular damage. Since the human placenta may be considered a highly vascular structure, rich in antigens closely related to human glomerular basement membrane, it is possible that such antigens, slightly altered, could enter the maternal body and act as an antigenic stimulus. In such cases the maternal human glomerular basement membrane might act as one of the most important and vulnerable target organs.

These preliminary experiments will be reported in greater detail elsewhere[12].

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ABNORMAL GLOBIN FORMATION IN HUMAN MEGALOBLASTS

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THE following work was undertaken to determine whether altered production of globin could be induced in human megaloblasts by exposing them *in vitro* to nucleoproteins derived from sickle-cell anæmia. More than thirty biochemically distinct characteristics have been successfully introduced into bacteria by exposing them to deoxyribonucleic acid (DNA) derived from homologous species[1]. Similar work on mammalian cells has been hampered by the obvious difficulties of using such cells as compared with bacteria and also by the difficulty of demonstrating that a successful transfer of genetic information has occurred. The abnormal hæmoglobins, however, provide an approach to such investigations. They are, at present, the only well-investigated system in human biochemical genetics where it can be shown that mutations produce demonstrable alteration in a protein molecule. Thus, Ingram has shown that sickle-cell hæmoglobin differs from normal hæmoglobin by the substitution of valine for glutamic acid in a specific peptide of the β-polypeptide chain[2–4]. Abnormal amino-acid sequences have now been shown for a number of genetic hæmoglobin diseases[5–8] and could therefore serve to indicate successful transfer of genetic information.

Megaloblasts were chosen because they are arrested at a primitive stage and might be susceptible to the influence of genetic material during maturation. Sickle-cell anæmia was chosen as a source of the nucleoproteins because it is the most readily available source of the genetic hæmoglobin diseases.

Marrow was aspirated from patients with sickle-cell anæmia, the DNA extracted with 2 *M* sodium chloride, deproteinized with deoxycholate and isolated by precipitation with 95 per cent ethanol. The final product was a highly viscous material containing 5–10 per cent ribonucleic acid and a similar amount of protein in addition to the DNA. No further attempt was made to remove these substances because of their potential contribution to transforming activity. This material was dialysed against 0·1 *M* sodium chloride and 0·05 *M* sodium citrate in the cold for 24 hr. and incubated with megaloblastic bone marrow. Each incubation mixture contained 10 ml. of sternal marrow aspirated from a patient with megaloblastic anæmia and 10 ml. of *S*-15 tissue culture fluid[9] which was supplemented by 5 mgm. heparin, 0·50 mgm. folinic acid, 0·10 mgm. vitamin B_{12}, 20,000 units penicillin and 0·12 μc. (80 μgm.) of ferrous citrate (iron-59).

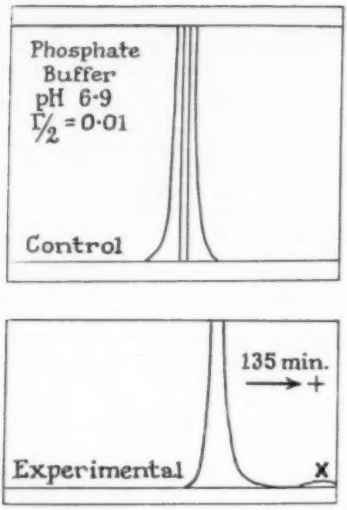

Fig. 1. Tiselius electrophoretic pattern of hæmoglobin derived from megaloblastic marrow incubated with and without sickle cell nucleoproteins. A single peak was observed in the control whereas an additional component (*x*) appeared in the experimental hæmoglobins. (Phosphate buffer, *p*H 6·9, ionic strength 0·1)

To the experimental flask was added 2 mgm. of sickle-cell nucleoproteins dissolved in 2 ml. of 0·9 per cent sodium chloride. The control incubation mixture was identical except that an equivalent volume of saline was substituted for the nucleoproteins. Incubation was carried out for 24 hr. at 37° C. with gentle agitation and the reaction terminated by the addition of deoxyribonuclease and 0·01 *M* magnesium sulphate. The cells were sedimented by centrifugation at low speed and w...ed 4–6 times, sedimenting each time from about 4 volumes of 0·9 per cent sodium chloride. The cells were lysed by freezing and thawing and the cell ghosts were removed by centrifugation at 30,000*g* for 30 min. The resultant hæmoglobin solutions were dialysed for 3 days against 0·001 *M* phosphate buffer, *p*H 7·2, with three changes of buffer followed by high-speed centrifugation. Altered hæmoglobin formation was detected by various electrophoretic procedures, ion-exchange chromatography and peptide analysis. An unexpected and consistent finding was that the radioactivity present in the hæmoglobin derived from marrow incubated with the nucleoproteins was 2–4 times that present in the control samples. Thus, in the experiment reported in this article, 0·8 per cent of the iron-59 added was incorporated in the control as compared with 2·35 per cent incorporated in the experimental.

The electrophoretic mobility of the hæmoglobins was first compared on either agar-gel or starch-gel and by moving boundary electrophoresis. Abnormal components were demonstrable in the experimental hæmoglobin solutions as compared with the control samples in five of nine experiments. One such component demonstrable by Tiselius electrophoresis is indicated in Fig. 1. Elution of an abnormal component from a carboxymethyl cellulose column[10] was achieved by establishing a *p*H gradient with 0·01 *M* phosphate buffer. This abnormal hæmoglobin component (III, Fig. 2) closely resembled sickle-cell hæmoglobin in its elution behaviour. No difference has been observed between control and experimental carboxymethyl cellulose elution patterns of hæmoglobin when megaloblastic marrow was incubated with DNA derived from normal marrow.

The abnormal component was concentrated by evaporation of the eluates, dialysed in the same manner as described, and a peptide analysis performed. Since there was no comparable peak in the control, the peptide composition of the abnormal component (III, Fig. 2) was compared with the peptide composition of hæmoglobins derived from peaks I and II in both the control and experimental samples. Peptide fingerprints of the hæmoglobins were carried out by the procedure of Ingram[4] using the modified digestion method of Anfinsen *et al.*[11]. Samples were run in pairs under identical conditions using the same quantity of hæmoglobin. Two peptides which are not demonstrable in any other fraction were present in the fingerprint of the abnormal hæmoglobin (*A* and *B*, Fig. 3). This peptide fingerprint does not, however, resemble that derived from sickle-cell hæmoglobin where the abnormal peptide is found in juxtaposition to peptide No. 4. Neither does it resemble the peptide pattern of fœtal hæmoglobin when compared with fingerprints of cord blood obtained by the same technique. An identical abnormal peptide pattern was obtained in another experiment of this type using similar conditions.

The possibility therefore exists that the megaloblasts can be induced to form a new hæmoglobin as the result of altered peptide synthesis and that therefore a phenotypic alteration or mutant has been produced. The electrophoretic behaviour of the abnormal component and its elution from carboxymethyl cellulose columns closely resemble those of sickle-cell hæmoglobin but the peptide analysis is distinctly different. It may be postulated that such a mutant could be

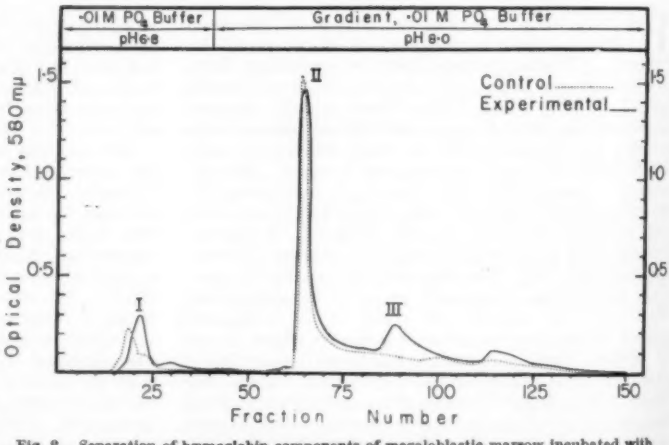

Fig. 2. Separation of hæmoglobin components of megaloblastic marrow incubated with and without sickle-cell nucleoproteins. Approximately 150 mgm. hæmoglobin described in Fig. 1 were introduced on to a carboxymethyl cellulose column (52 × 1·3 cm.) and the hæmoglobins separated by elution with 0·01 *M* phosphate buffer (*p*H 6·8–8·0). 4·0-ml. aliquots were collected at flow-rates of 20 ml. per hour. Hæmoglobin concentration was measured at 580 mμ. An abnormal component (III) was demonstrable in the 'experimental' as compared with the control

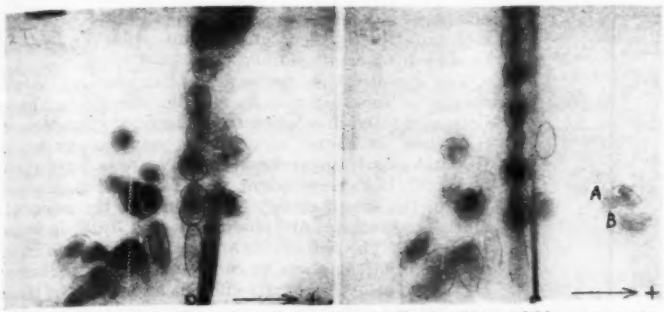

Fig. 3. Fingerprints of trypsin and chymotrypsin digests of hæmoglobin components separated on carboxymethyl cellulose columns described in Fig. 1. Paper electrophoresis of fraction II (left) and III (right) of the 'experimental' components applied at the origin (*O*) was carried out in the horizontal direction (cathode on the left), in pyridine/glacial acetic acid/water (10 : 0·4 : 90), *p*H 6·4 buffer, followed by paper chromatography in the vertical direction (ascending) using butanol/acetic acid/water (3 : 1 : 1) as solvent. Two peptides are demonstrable in the abnormal hæmoglobin component (*A* and *B*). No similar peptides were present in the other fractions

produced by nucleoproteins entering the cell and successfully competing or interfering with normal information transfer within the cell. (In unpublished experiments carried out in this laboratory, using similar culture conditions described here, influx of phosphorus-32-labelled DNA into rabbit marrow cells has been demonstrated[12].) It is unlikely that the abnormal hæmoglobins are due to artefacts such as denaturation or altered pigment formation since a distinctive peptide pattern has been observed in two experiments where fingerprint characteristics have been investigated. Experiments investigating the exact nature of the agent producing the change as well as structural considerations of the abnormal hæmoglobin are in progress.

In summary, abnormal hæmoglobin formation can be induced in human megaloblastic marrow cells exposed to nucleoproteins derived from sickle-cell anæmia. The data are not sufficient to identify with certainty either the product formed or the agent producing these changes. The electrophoretic behaviour of the abnormal hæmoglobin and its elution from carboxymethyl cellulose closely resembles sickle hæmoglobin, but the peptide analysis is distinctly different.

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MODE OF ACTION OF THE EFFERENT OLIVO-COCHLEAR BUNDLE ON THE INNER EAR

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THE Rasmussen olivo-cochlear bundle[1] represents the most peripheral part of a polysynaptic centrifugal system presumably responsible for control of acoustic input[1,2]. It originates in cells of the superior olive complex and terminates close to the organ of Corti in the inner ear[1]. Direct faradization of the bundle is known to depress acoustic evoked responses[3] and the results to be presented are concerned with the peripheral mechanism of this gating effect.

In experiments on cats (pentobarbitone, chloralose or high spinal section; middle ear muscles stapedius and tensor tympani cauterized; 'Flaxedil' infusion) the auditory nerve compound action potential (N_1) evoked by clicks and the cochlear microphonic potential (*CM*) evoked by tone pips have been recorded through an electrode placed on the round window. Trains of electrical pulses were applied to the crossed olivo-cochlear bundle through bipolar stereotaxic electrodes (Fig. 1*B*) at known intervals before delivery of the testing sound (click or tone pip) to the ear. As illustrated in the upper row of records of Fig. 1*C*, effective stimulation of the efferent bundle produces two effects, namely, inhibition of the N_1 spike[3] and potentiation of *CM* (ref. 4). Our observations suggest that both effects are genuine and that they are simultaneously produced by a chemical transmitter released from the olivo-cochlear axon terminals.

(*a*) *Parameters.* The two effects disclose proportional quantitative changes when the parameters of the preceding bundle stimulation are systematically modified. In the graph of Fig. 1*A*, trains of 1–28 pulses at 300/sec. were delivered to the bundle 10 msec. before the testing sound: changes in N_1 and *CM* appear after the train of 6 shocks and increase in parallel with the number of shocks.

(*b*) *Dissipation.* When the testing sounds are applied at increasing intervals after a standard train, of say, 20 pulses at 400/sec., N_1 suppression and *CM* potentiation appear maximal at the end of the bundle stimulation and dissipate exponentially with a time constant of about 0·15 sec.

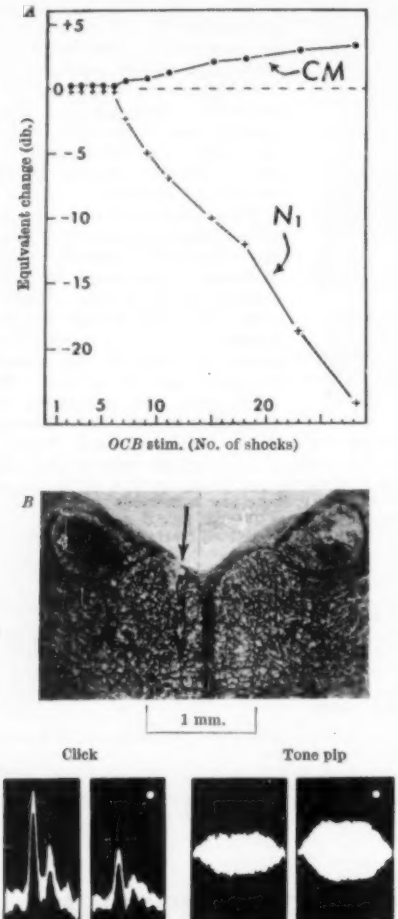

Fig. 1. Cat No. A295. Middle ear muscles cut. Clicks or 3 kc./s. tone pips, 30 db. above acoustic threshold, were delivered to the ear 10 msec. after delivery of a train of electric pulses at 300/sec. to the crossed olivo-cochlear bundle (*OCB*). *A*, amplitude changes in cochlear microphonic (*CM*) and neural (N_1) responses to sound as a function of the number of shocks in the preceding train delivered to *OCB*. *B*, histological control: section (modified Bielchowsky) with prussian blue mark of tip of stimulating electrode in *OCB*, between the two facial genua. *C*, oscillograms (several sweeps superimposed) showing suppression of N_1 spike and potentiation of *CM*, before and after strychnine. In the frames marked with a white dot, the sound was preceded by *OCB* stimulation

(*c*) *Neuropharmacology.* The intravenous injection of 0·05–0·15 mgm./kgm. strychnine sulphate which abolishes the N_1 inhibition[5] also eliminates the *CM* potentiation (Fig. 1*C*). The related alkaloid brucine produces the same antagonism to efferent bundle effects. No changes have been observed with metrazol, picrotoxin, ammonium chloride, eserine or dihydro-β-erythroidine.

For quantitative assessment, the changes in response voltage induced by bundle stimulation have been evaluated in relation to the intensity function of responses to sound alone. In many experiments the maximal suppression of N_1 was strikingly powerful, being equivalent to a 24-decibels attenuation of the sound energy. By contrast the maximal *CM* potentiation only amounted to a 3 db. increase (Fig. 1*A*). The two effects are thus of a quite different size, but both have to be considered when discussing the mode of action of the efferent axons on the inner ear and the following implications seem warranted.

(1) Since *CM* is generated in the hair cells of the organ of Corti[6,7] and is a 'receptor' potential[7], the recorded *CM* potentiation implies that the efferent axons must go as far peripherally as the hair-cell membrane. This is a useful cue for electron microscope studies.

(2) In view of the similar neuropharmacological properties, the efferent axons should manufacture and release the same inhibitory chemical transmitter as the axons responsible for post-synaptic inhibition in the cat's spinal cord[8]. Both inhibition of N_1 and potentiation of *CM* are ascribable to this transmitter (Fig. 1*C*).

(3) The olivo-cochlear suppression of N_1 being an obvious case of post-synaptic inhibition would depend on stabilization and possibly hyperpolarization of the terminal membrane of the afferent auditory axon since the latter represents the post-synaptic component in the excitatory afferent synapse between hair cell and auditory axon (Fig. 2).

(4) In order to account for the *CM* potentiation, we further suggest that part of the inhibitory transmitter is released on to the (pre-synaptic) membrane of the hair cell the resting potential of which would be increased by the usual selective change in ionic permeability. The *CM* receptor potential would thereby be potentiated since it is generated as a modulation of the hair cell resting potential (plus endolymphatic potential) by the acoustic transducer effect[6,7]. This would be the first evidence for a lack of restriction of transmitter effect to the post-synaptic membrane. Such a phenomenon might only occur in special and/or primitive synaptic organizations.

(5) The potentiation of the receptor potential is a paradoxical effect since the activation of the auditory axon by sound via the hair cell transducer is simul-

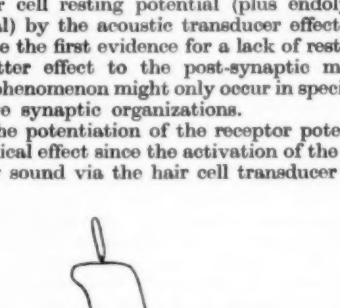

Fig. 2. Tentative diagram of synaptic organization in the organ of Corti, as suggested by the physiological evidence discussed. Electron microscope data would appear compatible with the occurrence of two types of axon terminals at the base of the hair cell, but the efferent endings have not yet been precisely identified

taneously prevented (effect mentioned in 3), and the net result of efferent bundle activation is to gate out auditory input to the brain.

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CELLULAR DOSE AND AGE OF HOST IN THE INDUCTION OF TOLERANCE

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THERE has so far been no systematic study of the relationship between antigen dose and age of host in the induction of tolerance of tissue homografts. In previous experiments[1] conducted with mouse strains differing at the *H*–2 histo-incompatibility locus a constant number of adult spleen cells (4–10 × 10^6) were injected into groups of mice of various ages and the decline of tolerance induction with increasing age was studied. This decline occurred in the first few days of life and was found to be very rapid: only 13 per cent of *A* strain mice injected on the 4th postnatal day with *CBA* spleen cells showed any significant degree of tolerance when skin-grafted 6 weeks later. This kind of approach is open to the objection[2] that the antigen dose does not keep pace with the increase in weight of the young recipients; our latest experiments, of which a preliminary account is given here, were designed to re-investigate the age-dependence of induction of tolerance with this objection in mind.

The mouse strains were identical with those previously used except that *CBA/A* hybrid cell donors were preferred to *CBA* donors in order to avoid the complications of graft-against-host reactions[1]. Spleen cells from hybrid donors were injected into 6 groups of *A* strain mice ranging in age from about 12 hr. to 13 days after birth. Each group comprised 16–20 individuals, and all injections were made intravenously. In the youngest groups the sigmoid sinus or the orbital branch of the anterior facial vein were used[1]; in the older groups, one of the lateral tail veins. The dose of cells was 5 × 10^6/gm. of body-weight (weight-adjusted dose) and the cell suspensions were prepared according to the method described previously.

All mice were grafted with female *CBA/A* hybrid skin 55 days after injection. The grafts were inspected 8 days later, that is, at a time when a first-set response can still be clearly distinguished from a second-set response, and they were observed for 100 days. The median survival time of control grafts (*CBA/A* hybrid skin on normal adult *A* strain mice) being 12½ days, the grafts were classified according to whether they survived for at least twice the mean survival time (25 days; Fig. 1) or 5 times the mean survival time (63 days; Fig. 2).

The results are set out in Figs. 1 and 2 alongside the original (*constant dose*) data of Billingham and Brent. They show very clearly that, in the first week after birth, the injection of a weight-adjusted dose gave rise to a consistently higher proportion of tolerant animals. For example, in the 4-day-old group the proportion of tolerant mice rose from 13 to 85 per cent, and even in the 6-day-old group it remained at a relatively high level (45 per cent compared with 0 per cent) (Fig. 1). Similar increases become evident when the data are plotted according to our more stringent criterion of tolerance (Fig. 2). Without doubt the use of a weight-adjusted dose added about 4 days to the period in which tolerance could be induced in this particular strain combination.

The second point emerging from these results is that the injection of a standard dose into 12- or 13-day-old mice did not lead to induction of tolerance in a single mouse; on the contrary, a small proportion

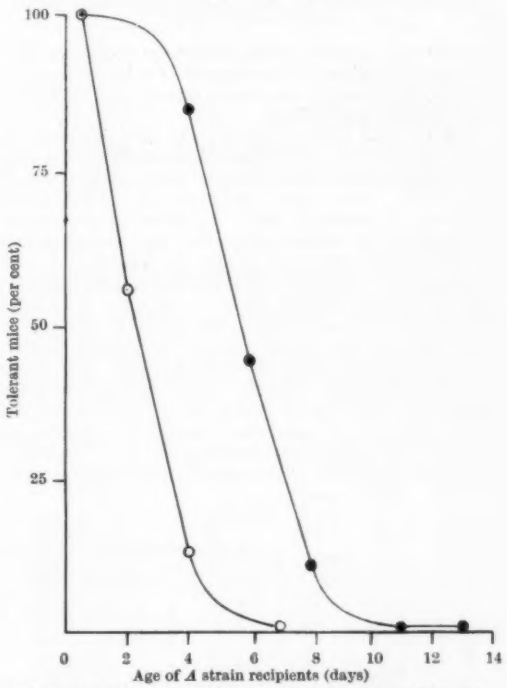

Fig. 1. Age-dependence of tolerance induction in *A* strain mice. Criterion of tolerance: skin graft survival at 2 × control median survival time (= 25 days). ○——○, 4–10 × 10^6 parental strain (*CBA*) cells per mouse. ●——●, 5 × 10^6 F_1 hybrid cells (*CBA/A*) per gm. body-weight

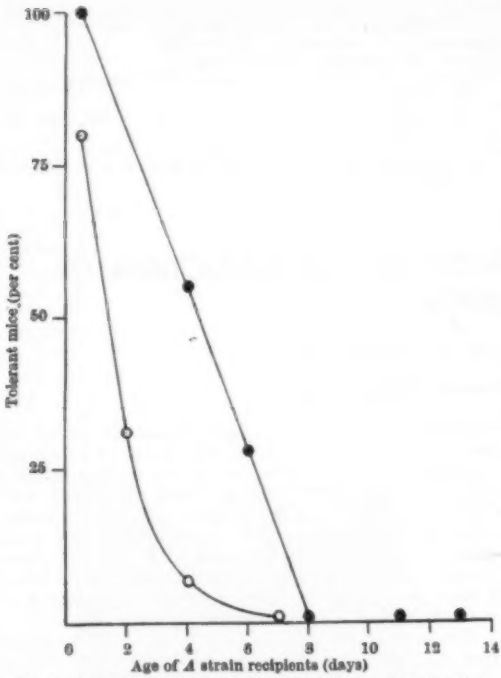

Fig. 2. Age-dependence of tolerance induction in *A* strain mice. Criterion of tolerance: skin graft survival at 5 × control median survival time (= 63 days). ○——○, 4–10 × 10^6 parental strain (*CBA*) cells per mouse. ●——●, 5 × 10^6 F_1 hybrid cells (*CBA/A*) per gm. body-weight

of these mice gave a weak second-set response, that is, they behaved as if the allogeneic (= homologous in the old terminology; see Gorer, Loutit, and Micklem[3]) cells had sensitized them.

The 11- and 12-day-old mice in the experiments described so far were injected with doses of cells which, scaled down according to body-weight, would have been more than adequate to bring about tolerance in neonatal mice. In order to investigate still further the relationship between tolerance and immunological paralysis groups of 12-day-old mice were injected with up to 10 times the weight-adjusted dose of *CBA/A* hybrid spleen cells (max. 3 × 10^6). The results are summarized in Table 1. Of the 26 mice not one was made tolerant by these massive stimuli and the mean survival-time of the grafts actually declined slightly with increasing dose, suggesting that larger numbers of cells sensitized more efficiently. (As the sensitivity elicited by allogeneic lymphoid cells declines relatively rapidly[4,5] a greater expression of sensitivity than that encountered by us could scarcely have been expected.) Hence, confrontation of these mice with a single cellular stimulus, however large, did not lead to the induction of tolerance.

Table 1

Exp. No.	Cell dose	No. of mice	No. of surviving grafts			Approx. MST (days)
			8 days	10 days	12 days	
6	WAD*	10	18	8	5	9½
8	3 × WAD	12	6	1	0	8
10	6 × WAD	2	2	0	–	
15	6 × WAD	7	3	0	–	8
17	4 × WAD I/V	5	2	1	1‡	
	6 × WAD I/P†					

* WAD, weight-adjusted dose = 5 × 10^6 cells per gm. body-weight = approx. 30 × 10^6 cells per mouse.
† I/p injection carried out on the following day.
‡ Graft destroyed by the thirteenth day.

It may be argued that the shift of the proportion of mice made tolerant in the first post-natal week is due to the fact that in Billingham and Brent's experiments parental strain cells rather than hybrid cells were used and that, in their experiments, the number of tolerant mice was therefore reduced by deaths from runt disease. Such an explanation is unconvincing, for a repetition of their experiments, using a constant number of *CBA/A* hybrid cells instead of *CBA* cells, is giving almost identical results. (This experiment is still in progress.) It is much more likely to represent a true shift produced by the higher antigen dose, an explanation which obliges us to revise our concept of the "neutral" period[6]. Such a period would appear to exist, if at all, only in a relative sense; it evidently depends not only on the degree of genetic affinity between cell donor and recipient[7,8] but also on the number of cells injected. In other words, immunological 'neutrality' for one antigen dose does not necessarily apply to another which is either larger or smaller—a conclusion which is in harmony with the observation that even new-born mice may be capable of immunological responses provided that they are stimulated by rather small doses of allogeneic cells[9]. That tolerance induction during the 'neutral' period should depend on antigen dose is perhaps not too surprising in view of the fact that induction of tolerance in new-born mice is also dependent on dose[1,9,10].

The point which stands out clearly from our results is that induction of tolerance in very young mice is not simply a scaled-down version of the kind of immunological unresponsiveness which can be brought about with soluble proteins in adult animals (for comprehensive reviews, see Chase and Smith[11,12]). Experiments somewhat similar in design but concerned with the induction of tolerance of bovine serum albumin in rabbits have been described by Smith[13], who found that with weight-adjusted doses tolerance could be elicited at birth or 7 and 14 days later, but not when injection was delayed until 21, 28 or 40 days after birth. (See also the work of Dresser[14] with mice.) Smith concluded that " . . . the induction of tolerance during the neonatal period depends upon special conditions which are unique to this period of life . . . ". Our own results are not at all at variance with this conclusion.

Nevertheless, it is possible to interpret our results by stipulating that the difference between the neonatal or very young mouse and the adult mouse is quantitative rather than qualitative. Such an alternative interpretation is prompted by findings reported from several other laboratories. (1) Tolerance of male isogenic grafts can be brought about in adult females by a single intravenous inoculation of approx. 20 × 10^6 male spleen cells[15]. (2) If donor and recipient differ only at the *H*–3 histocompatibility locus, adult mice can be sensitized or rendered unresponsive to skin grafts depending on the number of lymphoid cells injected[16] (1–5 × 10^6 cells sensitized, whereas 2 × 10^8 produced unresponsiveness). (3) Adult mice can be made unresponsive, even when donor and recipient strains differ at the *H*–2 locus, if they are injected intravenously and over a prolonged period of time with large numbers of spleen cells[17] (1·5 × 10^8 in 7 weeks).

These observations could be accounted for by the stem-cell theory of tolerance induction (see discussion

by Medawar[18]). This theory postulates that all immunologically immature cells are susceptible to induction of tolerance, regardless of whether they are in the embryo or adult. The exposure of adult animals to antigenic stimuli should therefore set in motion two processes: sensitization of mature cells and induction of tolerance in immature cells. Tolerance would normally be masked by the immune response, but if the sensitized cells were to be removed by some means (as for example by prolonged contact with the antigens) the lymphoid cell population of adult animals might be changed progressively from a predominantly sensitized to a predominantly tolerant one[19]. Although nothing is at present known of the specificity or the mechanism of the striking effect described by Shapiro *et al.*[17] (for example, is it due to central or efferent inhibition?) their experiments are open to this interpretation. That smaller genetic differences can be overcome by a much less-formidable antigen dose suggests the possibility that the number of sensitized cells involved in such a situation is considerably smaller.

Our own results also could be accommodated by the stem-cell theory, the neonatal or very young mouse being vastly more amenable to induction of tolerance across the *H*–2 barrier than the 'adolescent' or adult mouse precisely because its population of lymphoid cells is still predominantly immature. The occurrence of increasing numbers of immunologically mature cells in developing animals would therefore be sufficient to account for the age-dependence of induction of tolerance. The experimental evidence of Howard and Michie[9] certainly suggests that even the neonatal mouse may already have some immunologically mature cells.

This alternative interpretation, according to which the difference between unresponsiveness in adults and tolerance in neonatal animals would be one of strategy rather than of basic mechanism, is of course highly speculative. Simonsen's[20] observation that adult lymphoid cell populations may, in time, develop tolerance of the host's tissue antigens while retaining the ability to respond to the tissue antigens of other mouse strains suggests that it may not be well founded, but much depends on the elucidation of the mechanism which underlies this observation.

We wish to thank Prof. P. B. Medawar for his interest in this work and for his much-valued criticisms.

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EXCRETION OF UNCRYSTALLIZED URINARY CALCULI COMPOSED OF GLYCOLIPO-PROTEIN BY NORMAL AND MUSCULAR DYSTROPHIC MICE

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STRAIN 129 mice, susceptible to a hereditary myopathy[1], excrete urinary calculi examples of which are reproduced in Fig. 1. These bodies have been located *in situ*, floating freely in the urinary bladder, and are probably vesical calculi. They may appear either hyaline or opaque and sometimes exhibit bizarre forms. The largest calculi, the maximum length of which was 3·5 mm. (Fig. 1*C*), were obtained from two dystrophic male mice which were in a more advanced stage of the disease than any of the other animals tested, with the hind legs extended and non-functional. Calculus excretion by one dystrophic and one heterozygous normal animal began at about three months of age.

The rate at which the calculi are excreted is a function of sex and of the presence or absence of muscular dystrophy (Table 1). The results shown are for representative animals; however, all dystrophic males studied excreted calculi at a greater rate than any of the normal males, and normal females have never yet been observed to pass a calculus. Dystrophic females occasionally yielded tiny amorphous hyaline bodies.

Sections were prepared for histochemical examination by formalin fixation of the concretions followed by conventional paraffin block mounting, slicing

Table 1. RATES OF EXCRETION OF URINARY CALCULI BY STRAIN 129 MICE

Type of mouse	Sex	Age* (months)	Collection period (days)	Rate (calculi/ 10 days)
Normal (Homozygous)	M	5	61	1
Normal (Homozygous)	M	3	36	0
Normal (Homozygous)	F	3	36	0
Normal (Heterozygous)	M	5	36	4
Normal (Heterozygous)	F	5	29	0
Dystrophic	M	3	63	6
Dystrophic	M	—	61	13
Dystrophic	M	—	18	8
Dystrophic	F	5	36	0

* Age at which collection was begun.
—, age unknown but the mouse was in an advanced stage of dystrophy and died during the collection period.

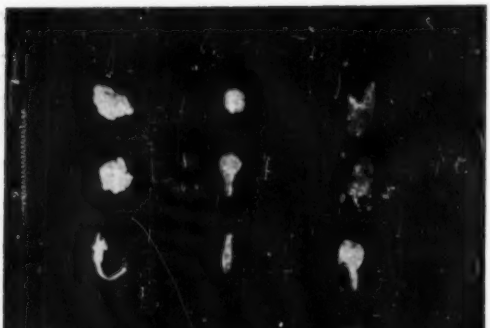

Fig. 1. Urinary calculi excreted by strain 129 mice. *A*, from homozygous normal mice; *B*, from 3–5 month-old male dystrophic mice; *C*, from male dystrophic mice in a more advanced stage of the disease. (× *c.* 2)

and staining techniques. Photomicrographs of portions of sections stained with various reagents are shown in Fig. 2. An outer wall was usually apparent and was defined best with hæmatoxylin and eosin stains (Fig. 2*A*). The portion of the wall shown is much wider than was generally seen but serves to illustrate certain small areas which stain blue with hæmatoxylin and appear dark in Fig. 2*A*. Since these areas did not react positively to Feulgen stain, they may represent minute zones of calcification rather than deoxyribonucleoprotein. The remainder and by far the major portion of the concretion showed only the light pink colour of the non-specific eosin. A strongly positive periodic acid–Schiff reaction (Fig. 2*B*) was shown throughout the calculi, indicating the presence of significant amounts of carbohydrate. Toluidine blue stain (Fig. 2*C*) showed thin sparse concentric rings of orthochromatic material only near the periphery while the remainder of the section reacted negatively to this stain suggesting that acid mucopolysaccharides are not essential for the formation of the calculi. Von Kossa stain for insoluble phosphates, carbonates and soaps gave a negative reaction and a sparse positive response was obtained to sudan IV at room temperature, suggesting small amounts of low-melting lipid. No evidence of a nidus with a separate identity was seen.

Water-insoluble protein comprised about 75 per cent of the original wet weight of the calculi and water-soluble solids about 8 per cent. To prepare the protein for chemical analysis, the calculi were ground in a mortar with distilled water and the insoluble residue was centrifuged, washed twice and dried to constant weight. Despite the fact that the availability of material has been quite limited, the use of sensitive micro-techniques has permitted qualitative identifications and quantitative estimates of its major constituents, and some of the more important results are reported briefly here. The complex protein exhibited an unexpectedly high nitrogen content (16·9 per cent in one batch assayed by digestion and Nesslerization[2]) and contained 1·5–2 per cent easily extractable lipid (four extractions of 30–45 min. each with 3 : 1 ethanol–ether at about 75° C.). About 20 per cent of the lipid was phospholipid as determined by conversion of inorganic phosphorus levels (methods of Fiske and Subbarow[3]) in lipid digests to 'average' phospholipid values according to Gortner[4]. Cholesterol, assayed by the method of Searcy and Bergquist[5], comprised approximately 10 per cent of the lipid. Both free and esterified forms were present but in varying ratio. Amide nitrogen, analysed in *N* hydrochloric acid hydrolysates (4 hr., 100° C.) by the Conway diffusion method[6], constituted about 1·3 per cent of the lipid-free protein. Carbohydrate was present to the extent of a few per cent although the values have varied with the

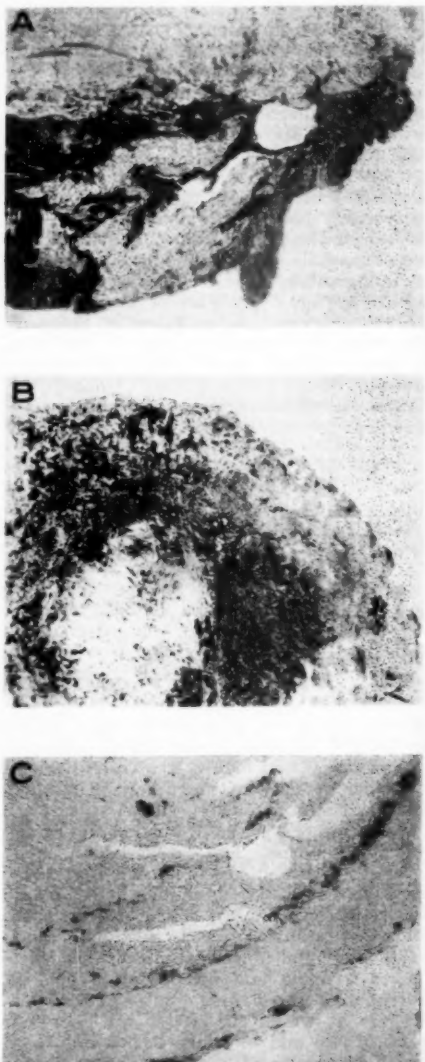

Fig. 2. Photomicrographs of outer portions of stained sections from urinary calculi. *A*, stained with hæmatoxylin and eosin; *B*, with periodic acid–Schiff reagent; *C*, with toluidine blue. (× *c.* 66)

orcinol[7-9] or anthrone[10] method used. Detection of free sugar spots on paper chromatograms of acid hydrolysates of the protein (3 *N* hydrochloric acid up to 21 hr., 100° C.) has not been achieved, possibly because of the low carbohydrate content, strong protein–carbohydrate bonds and/or sugar destruction. The major sugar was, however, identified as galactose by a spectrophotometric method[7] and the nature of the spectrum as well as ratios between extinctions at various wave-lengths[7] suggested the presence of lesser amounts of glucose. Similar criteria made probable the essential absence of ketohexose, mannose and pentose. The nature of the spectrum from the carbazole reaction[11] tended to eliminate hexuronic acid as a major constituent, while the presence or absence of hexosamine bound in the preponderant glycoprotein has not been definitely established. Both hexuronic acid and hexosamine may be present in the scant orthochromatic material or sections stained with toluidine blue. Sialic acid was essentially absent as judged by the observation that the tryptophan–perchloric acid test[12] yielded only a light colour, the intensity of which did not greatly exceed that obtained from an equal amount of beef serum albumin. The amino-acids of the protein moiety have been examined by 2-dimensional chromatography of acid hydrolysates (6 *N* hydrochloric acid, 24 hr., 100° C.) of the lipid-free material followed by ninhydrin development and visual comparison with spots given by an equal amount of bovine serum albumin of known amino-acid composition[12] which was hydrolysed in a manner identical with that used for the unknown protein. Several comparisons were made for each amino-acid and the average results were accepted as a reasonable basis for calculating approximate amino-acid composition. It was assumed that, for most amino-acids, errors associated with destruction or other variables were approximately the same for both preparations. Perhaps of most immediate interest here is the fact that the protein is characterized by unusually large amounts of serine. This substance was estimated to comprise approximately 15 per cent of the total amino-acid residue content on a weight basis. The glutamic acid content was also found high as compared with many proteins (about 20 per cent) and aspartic acid low (about 5 per cent). Cystine was quite low, but quantitative estimates are not justified because of large variability in the destruction of this amino-acid as a function of the carbohydrate content of the hydrolysis medium[14]. The levels of amino-acids did not vary significantly between batches obtained from normal and dystrophic animals. It is not certain whether there are other quantitative differences in the composition of the two types of calculi.

The mouse calculus material exhibits a chemical make-up which is markedly different from the organic matrix of crystallized human[15,16] or bovine[17] calculi and from a large number of mammalian proteins for which recorded data have been examined. The composition is similar in a general way to that of the Bence Jones protein with regard to the contents of phospholipid, cholesterol and carbohydrate[18] as well as the high serine-level[19] but deviates radically in the contents of other amino-acids. The significance of the influence of sex and of muscular dystrophy on the incidence of calculus excretion remains to be determined; however, beyond these considerations, it seems possible that the strain 129 mice may be a useful source of experimental animals for the study of calculus formation.

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MUCOPROTEINS OF BRONCHIAL MUCUS

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WARFVINGE[1] found that analyses of tracheobronchial secretions by electrophoresis on Whatman No. 1 paper in barbiturate buffer, *p*H 8·6, revealed at the most three mobile mucoproteins, the bulk of the material being absorbed at the origin. We have found that electrophoretic separation (16 hr.) on cellulose acetate foil (5 × 25 cm.) in citrate buffer (*p*H 5·1; μ 0·05) at 175–180 V. and 0·6 m.amp./cm. revealed as many as seven well-defined components having electrophoretic mobilities

Table 1. Electrophoretic Analysis of Bronchial Mucus

Patient	Diagnosis	*O*	A_1	Streak	A_2	*B*	*C*	*D*	*E*	*F*
1 ♂	Rhinorrhœa	28·8	—	6·4	—	35·3	4·1	9·7	15·9	0
2 ♀	Aspergillosis	7·4	10·4*	—	14·6	31·0	?	14·2	21·7	1·1
3 ♂	Hæmoptysis	8·2	8·1†	4·8	—	27·2	—	21·0	20·0	10·3
4 ♂	Hæmoptysis	15·1	—	7·4	—	31·8	—	38·9 (mainly *E*)		4·7
5 ♂	Pneumonia	8·6	5·8	7·2	—	28·6	—	21·5	18·4	9·9
6 ♂	Pneumonia	20·1	—	6·9	—	24·5	5·2	14·6	22·4	6·3
7 ♂	Bronchial asthma	12·5	—	4·1	—	19·1	—	52·6 (mainly *E*)		11·4
8 ♀	Pulmonary alveolar proteinosis	12·8	—	—	—	22·5	—	32·6	20·2	12·4
9 ♂	Chronic bronchitis (L.U.L. collapse)	14·3	—	15·2	—	9·6	—	53 (mainly *E*)		7·3
10 ♂	Chronic bronchitis	11·0	—	8·6	—	20·0	—	25·4	28	7·0
11 ♀	Chronic bronchitis	8·0	—	8·3	—	27·6	—	27·8	20·8	7·6
12 ♂	Chronic bronchitis	10·4	—	13·1	—	34·1	— ?	17·1	18·1	7·2
13 ♂	Chronic bronchitis	24·6	—	11·4	—	26·3	5·0 →	13·4	16·5	2·3
14 ♂	Chronic bronchitis	9·6	—	3·6	—	18·6	—	54·8 (mainly *E*)		13·8
15 ♂	Chronic bronchitis	34·3	—	13·3	—	9·9	—	21·9	7·9	11·9
16 ♂	Chronic bronchitis (and emphysema)	16·1	—	12·4	—	14·8	—	43·7 (mainly *D*)		12·1
17 ♂	Lung carcinoma and chronic bronchitis	19·3	—	16·8	—	15·4	12·4	26·7 (mainly *D*)		7·9
18 ♂	Lung carcinoma	17·3	17·5 ?	4·7	—	25·1	—	17·5	14·7	3·9
19 ♂	Lung carcinoma	16·2	— ←	26	—	18·4	—	14	18·7	6·7
20 ♂	Lung carcinoma	9·8	10·8	10·1	—	27·8	—	21·2	13·3	6·0
21 ♂	Lung carcinoma	9·4	13·7	13·1	—	21·9	5·4	21·3	13·5	1·4
22 ♂	Lung carcinoma	6·5	9·7	5·3	—	32·2	5·4	16·1	21·6	3·1
23 ♂	Lung carcinoma	24·7	—	11·4	—	16·3	6·3	17·4	21·4	2·8
24 ♂	Lung carcinoma	7·4	—	11·6	—	15·4	39·2 (mainly *D*)		6·4	20·1
25 ♂	Lung carcinoma	17·4	—	18·4	—	14·2	6·2	22·1	10·0	11·8
26 ♂	Lung carcinoma	14·4	—	7·4	—	28·4	10·6	23·3	13·2	2·7

* Mobility, 0·09. † Mobility, 0·19.

(M_F) A_1, 0·14 ± 0·04; A_2, 0·37; *B*, 0·57 ± 0·04; *C*, 0·67 ± 0·04; *D*, 0·79 ± 0·04; *E*, 0·88 ± 0·04; and *F*, 1 (9–10 cm. in 16 hr.). All components moved towards the negative electrode in the same direction as the endosmotic flow when the mucus was applied near (at 5 cm. distance) the Whatman No. 3 paper bridge (5 × 6 cm.) immersed in the anode vessel of an Evans Electroselenium apparatus. Strips were dried immediately with hot air and fixed in absolute ethanol. Components were revealed by dyeing (15 min.) with 0·5 per cent bromophenol blue in ethanol saturated with mercuric chloride, then washed with several changes of 2 per cent acetic acid[2]. They were estimated with an *EEL* scanner after clearing the strips with liquid paraffin in vacuum (3–4 hr.). For completeness the fractions absorbed at the origin *O* and others only discernible as a streak between A_1 and A_2 were also scanned and expressed as a percentage of the total applied. Components *B* and *E* had similar mobilities to serum albumin and γ_1-globulin, respectively. In samples of chronic bronchitis sputum and mucus only components *B*, *D* and *E* reacted with antisera to human serum proteins. The results obtained with various conditions are shown in Table 1. The bronchial mucus samples used were uncontaminated with saliva and obtained at bronchoscopy.

Components *B*, *D* and *E* appear in all mucus samples and, except in rare instances, are the three major components. Component *F* also appears to be a common constituent but can fall to very low levels. Only in the case of rhinorrhœa was it completely absent. Chronic bronchitis mucus samples present the simple patterns *B*, *D* and *E* and a generally high level of *F*. Invasion of the lung by carcinoma produces the additional components A_1 and/or *C*. Of the other cases, that of aspergillosis exhibits component A_2 uniquely and has an A_1 component of abnormally low mobility. Both these could be the metabolic products of the invading mould. Pulmonary alveolar proteinosis mucus contains an abnormally high content of component *D*.

A similar examination of sputum samples, of which the bronchial mucus would constitute a high proportion, showed the same overall picture. The cancer sputum samples (from seven patients) again showed additional components (usually *C*) not present in chronic bronchitis sputum and *F* was very low (1–3 per cent). Examination of sputa from one chronic bronchitic was commenced immediately after he had a 14-day course of tetracycline. The following day he started a 7-day course of chloromycetin and throughout the period under review was having bronchodilators, breathing exercises and vigorous physiotherapy. Following this treatment his general condition improved and his sputum gradually decreased from 2½ oz. to ½ oz. daily. Over a period of three weeks analyses showed a remarkable decrease of component *F* from 17·2 to 4·3 per cent. The neuraminic acid content of the sputum varied slightly over the same period from 1·23 to 1·39 per cent. Strips stained with the periodic acid–fuchsin sulphite reagent[4] showed positive reactions only with components *B*, *D* and *E*. Another chronic bronchitic with a carcinoma in the left hilar area maintained a high *F* content (9·5–21·5 per cent) throughout a three-week period of treatment with penicillin and achromycin.

An alternative method of analysis of the bronchial mucus samples involved the use of the immunological reaction in agar gel diffusion cells[5] with an antiserum raised against human serum proteins. Although no anti-*F* was present, it sufficed to distinguish the mucus of chronic bronchitis (3 lines) from that of patients suffering from bronchial carcinoma (4 lines), hæmoptysis (8 lines) and aspergillosis (at least 10 lines). Further development of this approach with additional antisera raised against component *F* and against selected whole mucus samples promises to afford a useful addition to methods of analysing bronchial mucus.

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ULTRASTRUCTURAL ALTERATIONS DURING THE CRABTREE EFFECT IN ROUS SARCOMA CELLS

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ELECTRON microscopic studies show that glucose selectively alters the microstructures of Rous sarcoma cells and that the cellular alterations observed could account for suppression of respiration[1] (Crabtree effect). The mechanism of glucose suppression of respiration of tumour cells has generally been approached through biochemical investigations[2]. Work in this laboratory indicates that glucose utilization *per se* does not depress uptake of oxygen. It was reported that increasing the concentration of glucose in the medium containing normal tissue will increase glucose utilization to a rate comparable with that of tumour tissue without suppressing respiration[3,4]. This preliminary report shows that when Rous sarcoma virus-induced tumours of the chorioallantoic membrane are excised from embryonated chicken eggs and incubated *in vitro* in the presence of glucose the cells undergo microstructural changes. Degeneration of mitochondria is observed. This effect of glucose on mitochondria of Rous sarcoma cells is similar to that reported by Merker *et al.* for Ehrlich ascites tumour cells[5]. Changes in the nucleus and endoplasmic reticulum of Rous sarcoma cells were also observed. These changes were not observed when Rous sarcoma was incubated in medium without glucose or in normal chorioallantoic membrane incubated in the presence or absence of glucose.

Standard lot *CT* 842 of Rous sarcoma virus was obtained from Dr. W. Ray Bryan and used for inducing tumours of the chorioallantoic membrane as previously reported[3,4]. Rous sarcoma was dissected free of non-tumorous tissue and sliced with a Stadie–Riggs hand microtome. Tissue slices were incubated under aseptic conditions in a Warburg flask in a final volume of 2 ml. with modified Hanks's balanced salt solution in the absence of added bicarbonate, and without phenol red indicator. The *p*H was adjusted to 7·6 with dibasic phosphate (*M*/15). The glucose concentration used was 5·5 μmoles/ml. Control flasks were without glucose.

After 12 hr. incubation at 37° C. tissues incubated with and without glucose were removed from the flask and immediately fixed in 1 per cent buffered osmium tetroxide[6] for 1 hr. at room temperature. The fixed tissue was embedded according to standard procedures in a 4:1 mixture of butyl and methyl methacrylates. Polymerization was carried out overnight at room temperature under an ultra-violet lamp. Sections were made with a Porter–Blum microtome equipped with glass knives.

Oxygen uptake was determined manometrically on tissue slices of tumour and chorioallantoic membrane. Results are reported on the average hourly rate of oxygen uptake during the 12th to the 16th hr. of in-

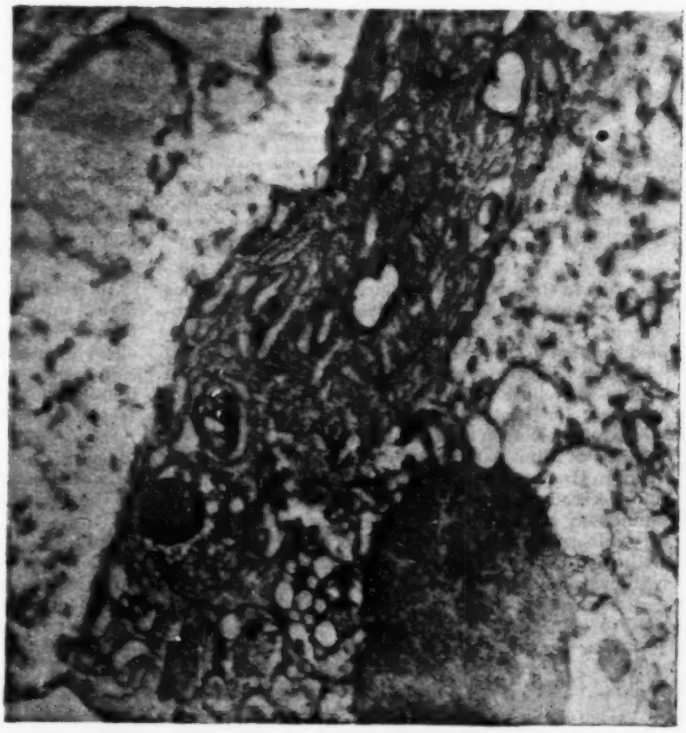

Fig. 1. Electron micrograph showing detail of a cross-section of a Rous sarcoma virus-induced tumour of the chorioallantoic membrane. Slices of tumour tissue were incubated in modified Hanks's balanced salt solution without glucose for 12 hr. at 37° C. The tissue was fixed in 1 per cent buffered osmium tetroxide and embedded in a 4:1 mixture of butyl and methyl methacrylates. The flattened surface cell shows mitochondria and cristæ and a well-delineated endoplasmic reticulum. Many vacuoles are present in the lower mesodermal cell and its nucleus shows a homogeneous composition. (× *c.* 16,500)

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Fig. 2. Electron micrograph showing a cross-section of Rous sarcoma virus-induced tumour of the chorioallantoic membrane. Slices of tumour tissue were incubated in a modified Hanks's balanced salt solution with 5·5 μmoles/ml. of glucose for 12 hr. at 37° C. The tissue was fixed in 1 per cent buffered osmium tetroxide and embedded in a 4:1 mixture of butyl and methyl methacrylates. The flattened surface cell and mesodermal cell give the appearance of being 'leached out'. The degeneration of microstructures is evidenced by marginal clumping along the nuclear membrane, no well-defined endoplasmic reticulum, and no well-defined cristæ in what appears to be the remains of mitochondria. (× *c.* 11,000)

cubation to show the physiological state of the tissues at the time samples were taken for electron microscopic studies. Results given in Table 1 were determined on tissue slices from the same tumour viewed by electron microscopy (Figs. 1 and 2). Respiration results on chorioallantoic membrane are similarly reported for sections from the same membranes viewed by electron microscopy.

Slices of Rous sarcoma which had been incubated 12 hr. in Hanks's balanced salt solution were examined by electron microscopy (RCA–*EMU*–2). Well-delineated microstructures were observed (Fig. 1). The cells selected show a cross-section of the tumour with regard to the surface of the chorioallantoic membrane. It is not known if the flattened surface cell is ectodermal or endodermal, but distinct mitochondria with cristæ are observable as well as a defined endoplasmic reticulum. The nucleus of the mesodermal cell has a homogeneous composition, but the cytoplasm shows greater vacuolation. Representative sections of other mesodermal cells show well-formed mitochondria even though the increased numbers of vacuoles in mesodermal cells distort the endoplasmic reticulum. A comparable section (Fig. 2) shows a cross-section of tumour slices which had been incubated for 12 hr. with glucose. The flattened surface cell as well as the mesodermal cell give a 'leached out' appearance. There is no defined endoplasmic reticulum, and the only evidence of mitochondria may be cross-sections seen in the mesodermal cell giving a degenerate appearance. The nuclei show marginal clumping and the 'leached out' appearance seen in the cytoplasm. More than 200 sections of tumour tissue that had been incubated in glucose were made and examined. No well-formed mitochondria were seen. The 'leached out' appearance of the cytoplasm and nucleus was present in all cells observed.

Comparable sections of normal chorioallantoic membrane, that do not give a Crabtree effect when incubated with glucose, appeared normal when examined under the electron microscope. In chorioallantoic membrane mitochondria were seen with well-defined cristæ, nuclei appeared homogeneous in composition, and the endoplasmic reticular system was well delineated.

It seems reasonable to propose that the physiological effect of glucose on Rous sarcoma respiration (Crabtree effect) may be a secondary result of the effect of glucose on the functional structures of the cell rather than a direct biochemical competitive inhibition. Damage to the cristæ of mitochondria results in 'leaching out' of enzymes and co-factors and respiration is interrupted[7]. It is proposed that glucose selectively induces damage to the mitochondria of Rous sarcoma cells and this may be the lesion of the Crabtree effect.

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Table 1. Average Hourly Rate of Respiration during 12–16 hr.

Tissue	Medium	Oxygen uptake (μl./mgm. dry tissue/hr.)
Rous tumour	BSS	5·2
	BSS + glucose 5·5 μmoles/ml.	1·8
Chorioallantoic membrane	BSS	6·3
	BSS + glucose 5·5 μmoles/ml.	6·1

Direct method of Warburg 2 ml. final volume of reaction chamber at 37° C. Tissue weight range, 3–5 mgm. dry weight. Chorioallantoic membrane was from a 16-day-old embryonated egg. BSS, modified Hanks's balanced salt solution.

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EFFECTS OF 2-DIETHYLAMINOETHYL 2,2-DIPHENYLPENTANOATE (SKF 525A) ON INSECTICIDAL POTENCY

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2-DIETHYLAMINOETHYL 2,2-diphenylpentanoate (SKF 525*A*) is well known to prolong the actions of a variety of drugs in mammals[1], and we have therefore investigated the effects of the compound on the toxicity to insects of pyrethrins and other insecticides, comparing its effects with those of the pyrethrin synergist 'piperonyl butoxide' (PB)[2,3]. SKF 525*A* has been administered to mammals in the form of its water-soluble hydrochloride, but when injected the hydrochloride proved inconveniently toxic to the test insects, and if applied externally could be expected to penetrate only slowly through the insect cuticle; hence we dosed the insects externally with SKF 525*A* in the form of the free base, which, like PB, was then non-toxic at the doses used.

In a series of qualitative tests, lesser mealworm beetles, *Alphitobius laevigatus* (F.), were dosed topically between the hind coxæ[4] with a solution of SKF 525*A* or PB, and 5–10 min. later with a solution of insecticide on the neck[5]. Separating the applications reduced the risk of chemical reaction between the basic SKF 525*A* and those insecticides that were acidic, before they had penetrated into the insect. 7 μgm. of SKF 525*A* or PB were applied in 0·07 μl. of solution in refined (odourless) kerosene, and an appropriate dose of insecticide in 0·025 μl. of solution in a heavier refined petroleum oil, Shell 'Risella 17'. Applications of insecticide without SKF 525*A* or PB were made comparably, with a dose of oil solvent on the other site. Use of the two different oil solvents enabled the two techniques of dosage to be used in conjunction. In additional qualitative tests, houseflies, *Musca domestica* L., were dosed topically[4] with pyrethrins or malathion, mixed with SKF 525*A* or PB, in solution in refined kerosene. Effects were determined by percentage of beetles paralysed 4 days after dosage (approximating to final mortality) and percentage of flies dead 24 hr. after dosage. The results, shown in Table 1, indicate a joint-action spectrum for SKF 525*A* qualitatively similar to that for PB; reduction by PB of the insecticidal activity of malathion in flies has been noted previously[6].

Table 1. EFFECTS OF SKF 525*A* AND PB ON THE TOXICITIES OF CERTAIN INSECTICIDES

Insecticide	*A. laevigatus*		*M. domestica*	
	SFK 525*A*	PB	SKF 525*A*	PB
Pyrethrins	+	+	+	+
Allethrin	+	+		
Barthrin	+	+		
Malathion	(−)	−	−	−
2-*n*-Valeryl 1,3-indandione	+	(+)		
2-*sec*butyl 4,6-dinitrophenol	0	0		
DDT	0	0		
γ-BHC	0	0		
Dieldrin	0	0		

+, Considerable synergism; (+), slight synergism; 0, no effect; (−), slight antagonism; −, considerable antagonism.

The synergistic effects of SKF 525*A* and PB on the pyrethrins were compared quantitatively. The synergist was used in mixture with the pyrethrins, in solutions in refined kerosene. The volume was 0·07 μl. per beetle, applied between the hind coxæ[4]; and 0·05 and 0·10 μl. per male and female fly respectively, applied dorsally on the thorax[4]. Factors of synergism[3,7] were determined, each the ratio of the ED_{50} for pyrethrins in the absence of synergist to that in the presence of synergist at 10 times the dose of pyrethrins. With SKF 525*A* the factor was 1·8 for the beetles and 2·5 for the flies; with PB the factor was 3·2 for the beetles and 15 for the flies. SKF 525*A* was less synergistic than PB.

Neither 2,2-diphenylpentanoic acid nor 2-diethylaminoethanol affected the toxicity of pyrethrins. Other congeners of SKF 525*A* are being investigated.

In mammals SKF 525*A* depresses the metabolism, especially oxidative metabolism, of numerous drugs, thereby increasing[1] or decreasing[8] their effectiveness according as the metabolic products are more or less active than the drugs themselves. In the present work SKF 525*A* depressed the effect of malathion, which is oxidized in the cockroach, *Periplaneta americana*, to the more insecticidal malaoxon[9]. O'Brien[10] mentions that SKF 525*A* failed to reduce the action on the cockroach and the housefly of certain organo-phosphorus insecticides with more insecticidal oxidation products, but does not state the conditions in his experiments. In the present work SKF 525*A* was found to increase the effectiveness of pyrethrins, which, like related pyrethroids, are metabolized in insects to less insecticidal compounds not as yet identified, though chromatographic evidence[11] indicates that they could be oxidation products. The influence of PB on the toxicities was qualitatively similar to that of SKF 525*A*. Thus the findings reported here are in general accord with other evidence[12] that PB and other 3,4-methylenedioxyphenyl compounds synergize pyrethrins in insects by depressing oxidative detoxification.

In mammals SKF 525*A* depresses drug metabolism brought about by the liver microsomes[1]; a scheme has been put forward[10] to account for the apparently low specificity of the enzyme systems involved. The present results suggest that there may be in insects systems analogous to those inhibited by SKF 525*A* in the liver microsomes of mammals.

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BLUE-GREEN ALGAE

Growth

IT is well known that many species of algae fail to thrive in simple inorganic media and may be cultured with greater ease in the presence of ill-defined organic materials such as soil extract[1,2]. These observations have promoted the suggestion that such algae may have requirements for growth factors, especially since many species are now known to be unable to synthesize certain vitamins essential to their metabolism[3]. In an earlier discussion of this question, however, Gerloff *et al.*[4] have directed attention to the fact that, in general, the addition of organic solutions of unknown composition has never been found to be absolutely essential for growth. They conclude that stimulation to growth under these conditions may be ascribed to the physiological condition of the algae rather than to the provision of some essential vitamin-like substance. Nevertheless, their statement that it is unlikely that any members of the Cyanophyta will be found to exhibit a requirement for vitamins has been shown to be in error in at least one instance by Pintner and Provasoli[5], who have discovered an absolute requirement for vitamin B_{12} by *Phormidium persicinum*. It is particularly interesting to note that several species of algae have been found not to thrive in the absence of other micro-organisms. In fact, Schramm[6] found himself unable to induce growth of zoospores and zygospores of *Vaucheria*, *Oedogonium* and *Spirogyra* in bacteria-free conditions. Among the Cyanophyta, Fogg[7] records the common observation that *Gloeotrichia natans* fails to thrive as well in pure as in impure culture. Findings such as these seem to support the assertion of Pringsheim[1] that "multiplication is often harder to achieve than isolation from bacteria and other unwanted micro-organisms". Similar experience and difficulties and the absence of more precise information led me to undertake the present work, the chief results of which are described here.

In isolating bacteria-free cultures of blue-green algae from rich soils of tropical northern Australia[8,9], observations were made with an unidentified species of *Nostoc* which agree closely with those for *Gloeotrichia natans* recorded by Fogg[7]. Growth of the alga in impure culture was clearly superior to that in pure culture. The stimulatory effect was found to be due to a species of the stalked bacterium *Caulobacter* which was prominent among the contaminants. When the two organisms were grown together in the light in a suitable nitrogen-free mineral medium, considerably greater amounts of nitrogen were fixed than by the alga alone under otherwise identical conditions. These results are shown in Table 1. It will be seen that, whereas 9·64 mgm. nitrogen were fixed by the alga in pure culture, 17·43 mgm. were fixed in the presence of the bacterium. In each case, a notable proportion of the nitrogen fixed was released into the culture solution. Separate tests showed that the *Caulobacter* is unable to fix nitrogen in pure culture. At the present time, there is no evidence to indicate that the stalk has any special function in the association comparable with the attachments shown by Houwink[10] to cells of *Bacillus*, although it has been found that the structure reaches maximal development in the presence of the alga and does not appear to be formed on media such as meat extract agar. It is worth noting that stalked organisms of the same genus have been found commonly in impure cultures of other blue-green algae from widely separate parts of Australia.

Table 1. Nitrogen Fixed (mgm.) by *Nostoc* alone and in association with *Caulobacter* (Kjeldahl analyses)

	Nostoc	*Nostoc* with *Caulobacter*
Cells	6·14	12·46
Culture solution	3·50	4·97
Total	9·64	17·43

To obtain greater understanding of the relationship, the stages in the growth cycle of the alga were followed in Petri dish culture. It was observed that hormogonia, on formation, move away from the colony margin and then undergo a series of reciprocal movements along the path first followed, this activity culminating in a sudden arching of the originally straight filament. At this stage, motility is lost and the individual cells begin to enlarge and divide in such a manner that the developing trichome becomes more and more contorted. Terminal and intercalary heterocysts become apparent, the latter being formed at fairly regular intervals along the trichome. The alga has never been observed to produce akinetes. Continued growth results in the formation of a roughly spherical trichome mass 0·1–0·2 mm. or more in diameter, from the interior of which a second generation of hormogonia emerges.

If single migrating hormogonia are transferred to fresh medium, their movements commonly cease, trichome formation begins almost immediately and the cycle of growth continues normally for at least a while. Frequently, however, the hormogonia either lose their pigmentation and die without further development or continue their normal growth and die at some later stage, often before the emergence of the second generation of hormogonia. Even when colonies 20–30 mm. in diameter are produced from a single hormogone, they are invariably pale in colour and thinly formed, and made up in large part of colourless and apparently non-viable trichomes. The capacity of hormogonia to continue developing has been found to be closely associated with the light history of individual colonies. Failure of hormogonia to develop on transfer may be induced most readily by frequent sub-culture under conditions of continuous and relatively intense illumination.

When small numbers of nitrogen-starved *Caulobacter* cells are added to single transferred hormogonia, growth is always more rapid than in the absence of the bacteria and is never accompanied by the death of the alga. Colonies produced in this way are larger, thicker and more densely pigmented than pure cultures and do not contain the colourless trichomes so characteristic of the latter.

Initially, it was supposed that some essential organic nutrilite might have been lacking in the absence of the bacterium, although this seemed rather unlikely in view of the fact that at least reasonably normal development was often observed to occur in pure culture as already described. None the less, the possibility was investigated. It was found that the incorporation in the basal nitrogen-free mineral medium of materials such as yeast extract, casein hydrolysate as well as the individual vitamins thiamine, biotin and B_{12} and a range of single amino-acids were without effect. Without exception, single hormogonia transferred to the supplemented media failed to develop. Similar results were obtained when

low concentrations of ammonia or nitrate ions were supplied. Even when growth took place in the presence of inorganic nitrogen, it was not superior to that in control plates.

Later, it was discovered that the addition of one or two drops of a 1 p.p.m. solution of indole-3-acetic acid was capable of effecting the recovery of bacteria-free hormogonia degenerated to the colourless condition preceding death. Accordingly, tests were conducted using *Avena* coleoptile sections in an attempt to detect growth-stimulating hormones in cultures of the alga and the bacterium. It was found that a highly significant increase in the length of coleoptile sections occurred in the presence of *Caulobacter* cells compared with controls. A similar response was recorded with sections in contact with a reasonably healthy pure culture of the alga grown for three weeks at only 12 ft.-candles and also with 18-hr. cultures, associated with *Caulobacter*, from which hormogonia were beginning to emerge at about 100 ft.-candles. In pure cultures more than 4 weeks old and grown at relatively high light intensities between 500 and 600 ft.-candles, the growth of coleoptile sections was significantly inhibited.

From these observations, there seems little doubt that, in some way, substances with hormone properties are necessary to enable the alga to achieve normal development. Here, attention is directed to a recent investigation in which Lazaroff and Vishniac[11] have concluded that *Nostoc muscorum A*, too, is dependent on a 'morphogenetic substance' to complete its normal cycle of growth. With *N. muscorum*, however, the substance is never limiting under normal conditions of cultivation in the light. Abnormal growth is exhibited only when the alga is incubated in the dark with a suitable source of carbon.

The inhibiting influence of older cultures on the growth of coleoptile sections is of interest. That the effect might have been caused by excess hormone seems improbable. It is known that auxin and indole-3-acetic acid are inactivated by light. Granick[12] has directed attention to the particularly destructive effect of blue light on auxin. In this connexion, it is relevant to note that the warm-white fluorescent lights used in the present work emit strongly in this region and have been found harmful to several species of chlorophycean algae by Algeus[13]. A more plausible explanation for the results is suggested by the separate observation by Algeus[2] that the oxidation products of indole-3-acetic acid are inhibitory to growth. However, it should not be overlooked that Stewart *et al.*[14] have found a precursor of auxin in radishes that exerts a similar effect.

Whatever the nature of the inhibitory substance or substances, it is possibly correct to assume that normal development of the *Nostoc* in question is dependent on the balance existing from time to time between hormone and growth inhibitor. As a corollary, it would be interesting to investigate the possibility that the reciprocal movements of hormogonia on agar media constitute a response to gradient concentrations of these substances around the margins of colonies.

In view of the fact that auxins tend to be destroyed in the light, it seems unlikely that the beneficial influence of *Caulobacter* is due solely to the contribution of a growth hormone, although this, undoubtedly, is of some importance. Other observations support this contention. In particular, the alga is invariably seen to be dark in colour, sometimes almost black, in the presence of *Caulobacter*, whereas pure cultures are commonly a pale green. The dark coloration is caused by phycoerythrin which appears to exercise a protective function by absorbing those wave-lengths to which the hormone is susceptible. Recently, Boney and Corner[15] have presented evidence to show that this pigment also has a protective function in certain red algae. The mechanism by which the bacterium stimulates phycoerythrin production by the alga is not known. Apparently light of short wave-lengths is also necessary, however, because the pigment is not produced under red light even with *Caulobacter* present.

In this matter, a further observation appears to be especially significant. It has been noted already that considerable enlargement of the trichome immediately precedes formation of hormogone. It seems not unreasonable to assume that such development might well be favourable to the conservation or build-up of hormone by the alga. If the beneficial influence of *Caulobacter* lay only in the provision of hormone, it would be expected that, in cultures containing the bacterium, trichome enlargement would be obviated to some extent. In fact, this is found to be true, although the effect is observed to operate only in the early phases in the growth of colonies from single hormogonia. Therefore, it must be concluded that direct stimulation is relatively short-lived and must be supplemented or replaced at some stage by hormone production by the alga with the protection afforded by abundant phycoerythrin.

A remarkable feature of the early growth of colonies containing *Caulobacter* is that fresh hormogonia are produced not only after minimal trichome development but also without the formation of heterocysts. The heterocysts appear to be associated with full trichome enlargement. Furthermore, it has been observed that hormogonia originating from fully developed trichomes always emerge from the interior of these bodies, never from the periphery. One is immediately reminded of a suggestion by Fritsch[16] that these 'enigmatic' structures might well be concerned with the production of substances controlling growth, cell division, and other developmental processes of blue-green algae. It is believed that the present work provides concrete evidence in support of this hypothesis and could also explain the reason why difficulty is sometimes experienced in securing the growth of algae in pure culture.

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Isolation of Bacteria-free Cultures from Hormogone-producing Blue-Green Algae

THE difficulties associated with obtaining bacteria-free cultures of blue-green algae are well known. Various techniques, involving the use of toxic physical

or chemical agents combined with patient and careful sub-culture, have been tested in attempts to eliminate contaminants. Of the many agents examined, few have proved to be successful. Allison and Morris[1], Allison *et al.*[2], Bortels,[3] Gerloff *et al.*[4], Fogg[5] and Venkataraman *et al.*[6] have prepared bacteria-free cultures by exposing algal material to ultra-violet light. Fogg[7] purified one species with the aid of chlorine water. De[8] depended on the selectivity of mineral media solidified with silica gel and on extensive sub-culturing to obtain pure cultures. Unfortunately, these techniques have not been found generally applicable[7,8], partly because a large degree of reliance must be placed on chance for success.

In these Laboratories, none of the techniques described in the literature proved satisfactory. A number of others, based on the assumption that an agent might be found to which the algae alone would be insusceptible, gave equally disappointing results. The possibility of using antibiotics has been examined[9], again without success.

In view of these results, it was felt that some technique aimed at the selection of newly formed and uncontaminated trichomes as suggested by Pringsheim[10] rather than the destruction of micro-organisms closely bound in the sheaths of older material might be more rewarding. Such an approach has, of course, already been used where final isolation has been from newly migrated hormogonia. However, the procedures used have seriously limited the chances of success. The method to be described was designed to minimize the operation of chance.

A small amount of inoculum containing a single species of alga is transferred to the surface of a suitable medium solidified with agar previously prepared as a deep, one-third filling a 6 in. × 1 in. culture tube. The material is incubated under appropriate lighting until fresh growth is just visible to the naked eye. Sufficient medium is then added carefully to form a plugging layer 3–5 mm. deep over the developing colony. As soon as this plug has set, 5–10 ml. of the same medium, but without agar, is added and the tube returned to the light room. With the algae under investigation, it was found possible and worth while to incorporate 60 μgm./ml. aureomycin in the plugging medium as an aid to final isolation. After some time, 5–11 days in my experience, young hormogonia and usually small numbers of motile bacteria are found to be present in the supernatant liquid medium although not visible to the naked eye. At this time, a series of small aliquots is transferred to Petri dishes and poured with the chosen medium. In these Laboratories, 10–20 0·1-ml. aliquots are used. The number of plates and the size of the aliquots are chosen to favour the development of isolated uncontaminated colonies. These are located as early as possible by regular microscopic inspection of the plates and immediately transferred to fresh medium. A fine hypodermic needle mounted in a suitable holder and a dissecting microscope have been found indispensable for this purpose. The purity of cultures is checked by normal cultural procedures and by direct microscopic inspection.

Up to the present, six bacteria-free cultures have been obtained, including the genera *Nostoc*, *Anabaena* and *Gloeotrichia*. It is of interest to note that the cultures of *Gloeotrichia* are being maintained on nitrogen-deficient media. Kjeldahl analyses suggest a capacity for nitrogen fixation.

Unfortunately, the technique described has not been found applicable to species which do not form hormogonia readily. However, recent investigations indicate that exposure of such organisms to suitable concentrations of indole-3-acetic acid at light intensities of about 12 ft.-candles may be generally useful for inducing formation of hormogone. In fact, using this technique recently, two further bacteria-free cultures have been obtained of algae that otherwise could not be induced to form hormogonia.

This and the preceding work have been supported by a University of Sydney research grant. Thanks are due to Miss R. Webb for technical assistance.

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Use of Antibiotics to purify Blue-Green Algae

The use of antibiotics in media for tissue cultures suggests that such techniques may also be useful for freeing blue-green algae of contaminants. Our results with antibiotics have not been entirely successful, but it may serve some useful purpose to report them here to avoid possible waste of time by other investigators.

The following substances are inhibitory to algal growth: cetrimide (*n*-cetyl-trimethyl ammonium bromide), dithionyl, streptomycin, neomycin, bacitracin. Actidione, penicillin, chloramphenicol, tetracycline, sulphafurazole, erythromycin, nystatin, novobiocin, oleamdomycin, polymyxin, furodantoin and fungostatin are not inhibitory. It is possible to eliminate fungal contaminants by cultivation of algae in the presence of actidione and fungostatin, but not possible to free the algae from bacteria by using singly any of the substances mentioned here.

The following combinations have been used without success: (i) tetracycline–chlorotetracycline; (ii) penicillin–erythromycin–aureomycin; (iii) polymyxin–penicillin–erythromycin–tetracycline. No success was obtained when the algal cultures were pre-treated with 0·002 per cent dithionyl.

It should be reported here that the bacterial contaminants are sensitive to antibiotics when tested in the absence of algae but cannot be eliminated when the algae are present. The algae seem to protect the bacteria against the antibiotics in some way. Also, some of the contaminants would not grow in ordinary meat infusion broth. Therefore, the absence of bacterial growth in broth should not be regarded as a sole criterion for purity of algal cultures.

We wish to acknowledge financial assistance provided by the Commonwealth Scientific and Industrial Research Organization Division of Land Research and Regional Survey and the Wheat Industry Research Committee of New South Wales.

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LETTERS TO THE EDITORS

PHYSICS

Vortex Shedding from the End of a Tube as a Result of Buoyancy Effects

One of the most interesting phenomena observed in fluid flow is that of vortex shedding, the best known example of which is the von Kármán vortex street behind a cylinder or similar obstacles normal to the flowing stream. For such two-dimensional systems, there is considerable information available. However, for axially symmetric systems, there appears to be little more than the recent results of Magarvey and Bishop[1] on spheres. Therefore, a study of vortex shedding in axially symmetric systems was initiated under Battelle sponsorship. In one system, vortices as shown in Fig. 1 were observed in alkaline water (containing amounts of sodium carbonate neutralized by up to 1·24 c.c. nitric acid/litre) discharging from a long vertical tube into a large plenum chamber. The chamber contained slightly acidic water (up to 7·65 c.c. nitric acid/litre). Reynolds numbers down to the experimental limit of above 200 were investigated. The flow pattern was revealed by phenolphthalein added to the inlet water supply.

The Strouhal number, vD/V, which characterizes in a dimensionless manner the vortex shedding frequency, varied from about 0·3 to 1·4 in the experiments. The Strouhal number was observed to increase with increasing acidity, with increasing alkalinity, and with decreasing Froude number. Reynolds number did not appear to be an important variable. It would appear that the buoyancy effects produced by the small release of heat at the reaction interface causes the vortex shedding in an otherwise stable flow. This supposition is supported by the observation of similar vortex shedding when a charged platinum ring at the tube exit was used to generate hydrogen bubbles, and when the density of the inflow was reduced slightly by use of a small addition of alcohol.

Fig. 1. Vortex formation at discharge of ½ in. diameter tube

One other observation should be reported. Tritton[2] observed, in an investigation of vortex shedding from rods, that at certain combinations of the independent parameters two alternative frequencies rather than one frequency could occur. Sato[3], in work on the instability of two-dimensional jets, made a similar observation. In my system, quite dissimilar to the previous two, we also observed that there were certain combinations of independent variables which led to two alternative frequencies, and, consequently, two alternative Strouhal numbers. In fact, the shifting from one frequency to the other, which often occurred in these instances, led to difficulties in obtaining accurate counts of frequency of vortex formation.

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Distribution of Pressure for Flow of Gas through Porous Media

The permeability coefficient K for flow of gas through a porous medium is defined by the equation[1]:

$$G = -K\frac{\partial c}{\partial x} \qquad (1)$$

where G is the flowing flux in moles through unit cross-sectional area of the medium in unit time, and $\frac{\partial c}{\partial x}$ is the concentration gradient. When the concentration of the gas is expressed in terms of the pressure p, equation (1) becomes:

$$G = -\frac{K}{RT}\frac{\partial p}{\partial x} \qquad (2)$$

If K is a linear function of pressure:

$$K = a + bp \qquad (3)$$

where a and b are constants, equation (2) may be integrated using the boundary conditions: $p = p_i$ (inlet pressure) at $x = L$; $p = p_0$ (outlet pressure) at $x = 0$; $p = f(x)$ $0 < x < L$ for all time.

The solution is:

$$p^2 + \frac{2a}{b}p - \left(\frac{a}{b} + p_m\right)2\Delta p\frac{x}{L} - p_0^2 - \frac{2a}{b}p_0 = 0 \qquad (4)$$

where $\Delta p = p_i - p_0$ = pressure difference, $p_m = (p_i + p_0)/2$ = mean pressure, and L is the length of the medium. This is the general equation for a parabola.

We have measured the pressure at three points inside a split specimen for steady-state flow of nitrogen, carbon dioxide and freon-12 (CF_2Cl_2) through Acheson '*A*' and Morgan '*EY9*' graphites. The experimental pressure distributions approximate to

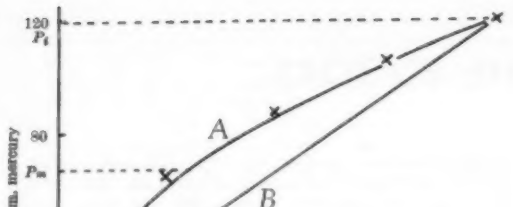

Fig. 1. Distribution of pressure through Acheson 'A' graphite specimen. Flow gas, nitrogen. p_i = 120·6 cm. mercury, p_o = 12·1 cm. mercury, L = 3·9 cm.; ×, experimental pressure. Full lines: *A*, parabola calculated from equation (4); *B*, chord

those predicted by equation (4) for $35 < \Delta p < 160$ cm. mercury and $20 < p_m < 120$ cm. mercury. A typical distribution is reproduced in Fig. 1. In practice, the experimental pressures diverge from the theoretical parabola by up to 12 per cent at the centre of the specimen, the experimental error being less than 3 per cent. This divergence may be attributed to three possible causes: (1) inhomogeneity in the graphite (the variation in K through specimens of the two graphites was 30 per cent and 55 per cent respectively); (2) non-linearity of the dependence on pressure of K (in one of the graphites $K = 0{\cdot}25 + 0{\cdot}065\,p - 7 \times 10^{-4}\,p^{1{\cdot}48}$), and (3) possible surface flow of adsorbed gas.

Carman[1] gives the integration of equation (2) as:

$$G = \frac{K}{RT} \cdot \frac{\Delta p}{L} \qquad (5)$$

which he states is valid when Δp is small or K is independent of pressure. Now it may be readily shown from equation (4) that the tangent to the theoretical parabola at $p = p_m$ is parallel to the chord from p_i to p_o, that is, at $p = p_m$, $\frac{\partial p}{\partial x} = \frac{\Delta p}{L}$. This means that (5) may be applied to calculate K at the mean pressure in a porous medium for any Δp provided that K is a linear function of pressure.

Biram[2], in a recent communication, has proposed that the constants a and b in equation (3) can be obtained by measuring the pressure at the mid-point and at both ends of a specimen. The equation he gives may be derived from equation (4). In practice, we find that his method may involve an error as high as 120 per cent due to the reasons mentioned earlier which cause deviations of the experimental pressures from the theoretical parabola.

We also take this opportunity to mention that we have observed minima in the variation of K with pressure for several gases in different graphites at low pressures.

We are indebted to Mr. A. McNab of the New Zealand Department of Scientific and Industrial Research for a helpful discussion. We acknowledge the support of the Australian Atomic Energy Commission in the award of a scholarship to one of us (G. J. F.), and the provision of graphite samples.

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The Reaction Silicon-29(*n*,α)Magnesium-26 at 14 MeV. Neutron Energy

A 400 Ω-cm. *n*-type silicon surface barrier detector was irradiated by neutrons of energy 14·03 ± 0·05 MeV. The experimental arrangement is identical with that described in an earlier communication[1] reporting results for (n,α) and (n,p) reactions in silicon-28 at the same neutron energy.

The reaction silicon-29(n,α)magnesium-26 has a Q-value of − 0·022 MeV., so that although its abundance in natural silicon is only 4·7 per cent it is possible to observe the reaction in competition with the more intense silicon-28 reactions, as the typical energy spectrum of Fig. 1 shows.

The results of Hinds and Middleton[2] for the energy-levels of magnesium-26 enable assignment of the two highest energy groups to the magnesium-26 ground-state and the excited state at 1·801 MeV. The ground-state and first four excited states of magnesium-25, populated by the silicon-28(n,α)magnesium-25 reaction, are also present and are labelled.

Dearnaley and Ferguson have examined the reaction silicon-29(n,α)magnesium-26 in the nuetron energy-range 5–8 MeV., and report a group which could correspond to transitions to a new first excited state in magnesium-26, located at 1·33 MeV. (ref. 3). Re-examination of the high-energy portion of our previously reported spectra did not yield evidence

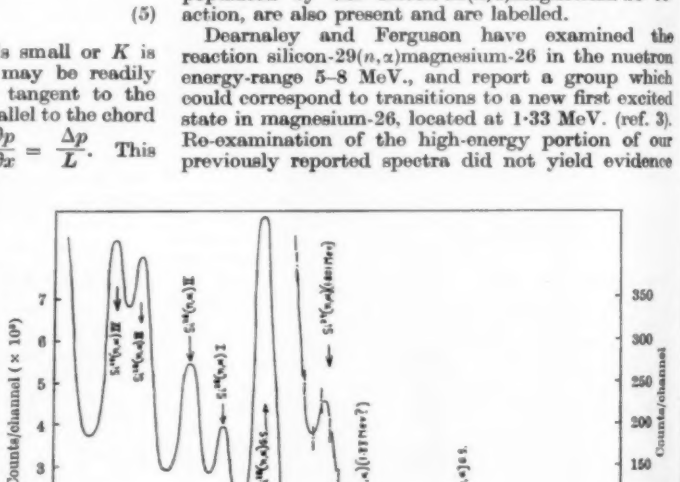

Fig. 1. Spectrum showing the reaction silicon-29(*n*,α)magnesium-26

for such a transition. Re-investigation of the relevant region with improved statistics was undertaken with the results given above, and fails to provide evidence for an alpha-particle group corresponding to the level postulated by Dearnaley and Ferguson.

The approximate cross-section ratio for the magnesium-26 ground-state and 1·801-MeV. excited state groups, obtained in the present experiment, agrees with that obtained by Dearnaley and Ferguson at 7·6-MeV. neutron energy. In the absence of a selection rule inhibiting the transition, one would expect the 14 MeV. (n,α) spectrum to exhibit a cross-section to the new magnesium-26 level similar to the ground-state cross-section. Fig. 1 indicates that this is not so, and if the level exists the cross-section for the transition to it is less than 0·1 mb.

Previous investigations of the energy-levels of magnesium-26, notably those of Hinds and Middleton, using the reactions magnesium-25(d,p)magnesium-26, aluminium-27(t,α)magnesium-26 and magnesium-24(t,p)magnesium-26, gave no indication of a level in magnesium-26 at 1·33 MeV., nor did the experiment of Glover and Weigold[4], investigating the reaction aluminium-27(n,d)magnesium-26.

Dearnaley and Ferguson have considered and investigated possible sources of contamination and we can offer no obvious explanation for the peak observed in their results. Additional experimental evidence is required to resolve the problem of whether or not the postulated level exists.

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GEOCHEMISTRY

Origin of High Tritium Content of Atmospheric Methane, Hydrogen and Stratospheric Water

Recent work (ref. 1 and Suess, H. E., private communication) has shown that atmospheric methane has a fractional tritium content orders of magnitude higher than that of rain water and approaching that of atmospheric hydrogen and stratospheric water. The rate of increase with time of this tritium in methane makes it appear likely that it originates in the testing of nuclear devices. (The finding by Bishop *et al.*[1] that the specific activity of atmospheric methane appears to be lower in the troposphere than in the stratosphere or at the surface is, however, not obviously explained on the basis of origin in thermonuclear explosion, or for that matter by origin from any single source.) However, no satisfactory mechanism by which such tritium can be incorporated in methane has been advanced. The high temperature and oxidizing conditions supposed to exist in the bomb fireball seemed to rule it out as a source of tritiated methane[1]. Biological processes yielding methane of high specific activity are difficult to conceive; and indeed, sewage methane has little tritium content[1]. High atmosphere, radiation-induced mechanisms for exchange of methane with high specific activity atmospheric hydrogen can be formulated, but these mechanisms suggest that the methane is likely to be oxidized under the conditions required (Libby, W. F., private communication).

The thesis of this communication is that tritiated methane may after all be produced in the fireball, in a reducing atmosphere which I believe must exist at its centre. Thermonuclear weapons are presumably constructed primarily of reducing substances. Following detonation, the hot gas formed from bomb material will push back the surrounding atmosphere to form a reducing core within the fireball. On cooling to about 3,000° C. this core will contract to a diameter approaching 100 metres, assuming some reasonable mass of the original weapon. During this stage the fireball is isothermal[2], and it is very unlikely that the large reducing core will mix with its oxidizing surroundings. On further cooling its contents will form molecular species. The tritium may be expected to combine largely as metal hydrides, molecular hydrogen, water, ammonia and hydrocarbons including methane. (The necessary carbon may be derived from conventional explosives and any other carbonaceous material contained in the device.)

At the end of the glowing, isothermal stage the reducing core, now hotter than its surroundings, will presumably tend to rise. During this convection, air will be entrained and the cooling, shrinking bubble of reducing gas may be expected to break up and mix. Insufficient data are openly available to speculate about how much combustion will occur during this process, but it would be surprising if such oxidation were complete.

If the high tritium content of atmospheric methane is due to this mechanism the question arises why this same methane does not also have a high carbon-14 activity[1]. It must be first pointed out that most of the carbon-14 from the $^{14}N(n,p)^{14}C$ reaction will be produced outside the reducing core and will therefore appear as $^{14}CO_2$. However, even if the amount of carbon-14 within the core were of the same magnitude as that of tritium, then atmospheric methane resulting from such events having an activity of 2×10^4 tritium units ($T:H = 1:5 \times 10^{18}$) would have incremental carbon-14 activity amounting to only about 10 per cent of that of contemporary biosphere carbon.

The hypothesis of a reducing core in a nuclear explosion fireball also suggests that the high tritium content of atmospheric hydrogen[3] of the thermonuclear era arises directly, and is not dependent on, an exchange between molecular hydrogen and tritiated water. Most of the tritium in the fireball will probably be combined in molecular forms other than methane and hydrogen, particularly in metal hydrides. These, and hydrocarbons less stable than methane (for example, acetylene), will afterwards be completely oxidized in the atmosphere to yield water vapour of high specific activity found in the stratosphere[4].

The validity of the suggestion advanced here may be checked in several ways. The most direct involves sampling the fireball gases soon after they have cooled. Later tests on atmospheric gases may be based on the abnormally high ratio of deuterium to protium which may be presumed to exist in the fireball core.

Thus there should be an unnaturally high probability that a molecule of atmospheric methane containing tritium contains a deuterium atom as well. Such a measurement of the ratio $CH_3T:CH_2DT$ will require mass separation prior to the application of low-level counting techniques. The ratio of HT:DT in atmospheric hydrogen is much easier to determine since these isomers can be separated by gas chromatography[5]. The answer here will depend not only on the origin of the tritiated hydrogen, but also on whether it can undergo exchange with atmospheric water.

I am indebted to Prof. W. F. Libby and to Dr. E. A. Martell for stimulating discussions of the present proposal. This work was supported by the U.S. Air Force and Atomic Energy Commission.

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Formation of Pegmatitic Carbonatite in a Syenite–Marble Contact

Immediately north of the village of Karacayir, vilayet Sivas, Turkey, a small intrusion of rather coarse-grained syenite occurs in a banded marble formation of unknown age. Here I had occasion to study in some detail a peculiar coarse-grained marble of pegmatitic appearance, containing biotite and apatite. The banded marbles seem to be regionally metamorphosed, on which the thermal metamorphism caused by the intrusion is superimposed. The part of the marble which protrudes into the syenite is changed into a carbonatite–pegmatite. Otherwise the marbles retain their regular banding, which even seems to be accentuated when nearing the contact. Within the aureole of thermal metamorphism small crystals of phlogopite and diopside develop in small amounts on the stratification planes as well as throughout the marble. Near the contact small dikes of syenite–aplite and more-or-less crushed syenite–pegmatite cut through the marbles; the syenite itself contains locally muscovite.

A non-metamorphic fossiliferous impure nummulitic limestone lies unconformably on top of both marble formation and syenite, thereby defining the age of the latter as pre-Eocene. Intra-formational conglomerates are polymixt, containing quartz-pebbles, quartzites, quartzitic schists and acid intrusives.

Next to calcite the pegmatitic carbonatite contains large (up to 1 in. and more) biotite crystals, slender hexagonal prisms of green apatite, and locally small idiomorphic thorianite (ThO_2) crystals. In one place a mass of large idiomorphic allanite crystals has been found, of platey habit, up to 1 in. across. Direct evidence that this carbonatite actually passed through a molten state is not available, as no carbonate-glass was found. Wyllie and Tuttle[1] state that: "Some carbonate liquids can be quenched to a glass by extremely rapid cooling, but in nature such rapid cooling is unlikely and evidence of melting in rocks will be difficult to find".

The total obliteration of the pre-intrusive structure of the marble, the idiomorphic and coarse-grained habit of its constituent minerals, its obvious permeation with magmatic fluids (addition of thorium, rare earths, phosphorus pentoxide, (Fe,Mg)O, silica and water) indicate a pseudo-liquid condition of this carbonatite mass at the time of the syenite intrusion. This condition is most probably caused by the presence of a liquid phase, a carbonate melt.

According to the same authors[1] the partial melting of carbonates in the presence of water vapour starts at temperatures as low as 650° C., and at pressures reached at relatively high levels in Earth's crust. This temperature is almost certainly exceeded during the intrusion of a syenitic magma. In another publication Wyllie and Tuttle[2] state that: "Although calcite is generally the dominant mineral in carbonatites ... apatite and mica are constant accessories". The presence of radioactive and rare-earth minerals (thorianite and allanite) in the carbonatite mass shows its close affinity to 'normal' intrusive carbonatites. It is believed, in the light of the results obtained by Wyllie and Tuttle[1,2], that pressure-temperature conditions in this contact provoked the (partial) liquefaction of the marble, which recrystallized on cooling as a pegmatitic mass of carbonatite composition. The importance of this example lies in the fact that here a carbonatite, associated as usual with alkaline intrusives, is still indisputably recognizable as the direct continuation of a sedimentary marble. Though I certainly do not claim definitely that carbonatites must be formed this way, it shows at least that they may.

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METALLURGY

Embrittlement of Grain Boundaries by Equilibrium Segregation

Equilibrium segregation of impurities or solute elements has frequently been suggested as a cause of grain boundary embrittlement in metals and metallic compounds, but the evidence has been largely indirect. Even if the existence of grain boundary segregation be granted in specific instances, the manner in which such segregation might give rise to embrittlement has remained wholely speculative. It is the purpose of this communication to report that in a large number of cases where boundary segregation is established, suspected, or possible, a significant hardening of the grain boundary region relative to that of the interior of the grain is observed by microhardness measurements.

A typical result is shown in Fig. 1 for a high-purity iron sample treated by Ainslie *et al.*[1] in a sulphur-bearing atmosphere and demonstrated by them with tracer techniques to contain sulphur absorbed in grain boundary regions. This case appears to be the most firmly established instance of equilibrium grain boundary segregation on record. Tests on a com-

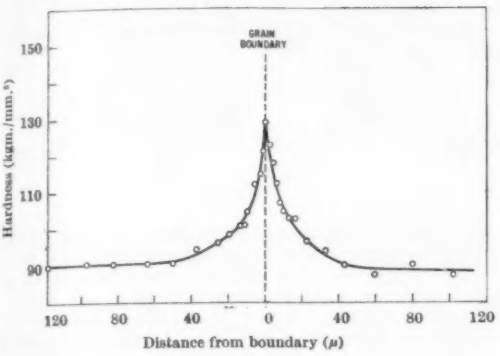

Fig. 1

panion sample which had been subjected by Ainslie *et al.* to identical heat treatment in sulphur-free atmosphere showed no boundary hardening whatsoever. The intensity of the peak hardening in the sulphur-segregated iron (about 40 per cent), and the extent of the measurable effect (about 50μ either side of the boundary) are typical, but hardness differences of as much as 60 per cent and breadths as great as 100μ on each side have been observed in some cases with other systems. Although effects of relative orientation of grains undoubtedly exist, they appear to be small since comparable hardening is observed in all boundaries of a randomly oriented polycrystalline sample.

Table 1 lists some of the cases in which grain boundary hardening by equilibrium segregation has been observed in the present investigation. Later publications will report these results in more detail.

Table 1

Base material	Suspected segregant	Typical $\frac{\Delta H}{H}$ %	References suggesting segregation or reporting embrittlement by trace amounts of impurity
Iron	S	43	Ainslie *et al.* (ref. 1)
Iron	O	30	Low and Feustel (ref. 2)
Aluminium bronze	Al	13	Perryman (ref. 3)
Beryllides	O and/or N	50	Lewis (ref. 4)
Silicides	O and/or N	33	Fitzer (ref. 5)
Miscellaneous intermetallics, for example, AgMg, NiAl, Ni_3Al, CoCr-σ, Ni_3Ti, etc.	frequently O and/or N	15–60	Westbrook and Wood (unpublished work)

Our experiments show certain features which appear to be common to the general phenomenology of the effect.

Among these are:

(1) Segregation is dependent on temperature. In some instances, segregation, and therefore grain boundary hardening, disappears at high temperatures. It is therefore possible, in favourable circumstances, to eliminate segregation and improve toughness by quenching.

(2) Segregation is frequently modified by the presence of another trace impurity, for example, segregation of oxygen does not occur in iron bearing small amounts of carbon but only in decarburized iron.

(3) Grain boundary hardening by segregation in intermetallic compounds seems only to occur when there is a stoichiometric excess of a chemically active element.

(4) Kinetics of segregation and desegregation are extremely rapid, suggesting lateral transport of segregant along some 'short circuiting' diffusion path.

Previous suggestions for mechanisms of grain boundary embrittlement by segregation have involved internal stresses, changes in melting point, and changes in surface energy. While all are conceptually plausible, no such mechanism has had unambiguous experimental support. It is now clear that in a large number of cases embrittlement results from the creation of a barrier to dislocation propagation by formation of a hardened region at and near the boundary. Whether this hardening occurs by a solution hardening mechanism or by changes in the dislocation density and structure at and near boundaries is not yet certain and the particular source of hardening may well vary from one case to another. In the particular case of iron-sulphur, the extensive networks of dislocations adjacent to grain boundaries revealed in the transmission electron micrographs of Ainslie *et al.*[6] are adequate to account for the observed boundary hardening.

We are grateful to Messrs. N. G. Ainslie, E. A. Aitken and J. R. Low for the loan of samples, to A. J. Peat for assistance, and to J. R. Low, A. U. Seybolt and D. Turnbull for helpful discussion.

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Stress Concentration Effects in Tertiary Creep

In most cases, fracture under high-temperature creep conditions results from the formation and linking up of small voids on the grain boundaries within the metal. A period of accelerating creep precedes the fracture and it is generally assumed that this acceleration is caused by the reduction in stress-carrying area through the formation of these voids[1,2].

It has recently been shown that the density of a material during creep decreases at an approximately linear rate up to the onset of tertiary creep but thereafter decreases at a continuously increasing rate until fracture ensues[3]. If stress concentration is the cause of tertiary creep, the reduction in cross-section must have increased the stress to a value which gives a detectable change in the rate of deformation at this stage. Clearly the dependence on stress of the rate of creep will then be an important factor in determining when this increase in creep-rate will be detectable and also in the rate of acceleration to fracture, that is in the fraction of the total time to rupture which is spent in tertiary creep.

Some recent work[4] on nickel alloys containing only 0·012 wt. per cent of tin is significant in this respect. When tested at 400° C. this material is extremely dependent on stress, a stress increase of 10 per cent giving an increase in minimum creep-rate and a decrease in fracture-life by a factor of 10^3. On the basis of a stress concentration mechanism for tertiary creep it might therefore be expected that a

very rapid acceleration to fracture would be observed at an early stage of creep. However, this is found not to be the case. The shape of the creep curves for this material is very similar to those for pure nickel at this temperature and similar to tests on the same material at higher temperatures where no large stress-dependent effects are observed.

Considerable necking occurred before fracture at 400° C., but this must have occurred at a late stage of tertiary creep since only a small amount of necking would have been sufficient to give almost immediate fracture with a material having such a stress-dependent creep-rate.

We conclude, therefore, that stress concentration, effected by void formation or necking, is not important in causing the acceleration in creep-rate before fracture.

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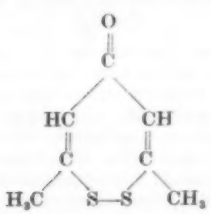
CHEMISTRY

Crystal Structure of 2,5-Dimethyl-Dithio-Furophthene, a Homologue of Thio-Thiophthene

During work on a series of sulphurated cyclic compounds[1], we have determined the structure of a substance to which formula I was previously ascribed.



(I)

The substance crystallizes from toluene as yellow-orange prisms, often twinned, belonging to a monoclinic system, space-group $P2_1/c$; four molecules are in the unit cell of dimensions:

$$a = 4{\cdot}44 \quad b = 10{\cdot}78 \quad c = 17{\cdot}20\ \text{Å}. \quad \beta = 97° 20'$$

Observed density 1·40 gm.cm.$^{-3}$; calculated 1·42.

Single-crystal precession and Weissenberg photographs enabled us to carry out X-ray analysis on both (100) and (010) projections. We determined the structure not with a heavy-atom method but using Sayre's direct method[2]. The usual refinement process, based on a few Fourier and difference syntheses, gave the present values for the reliability index, $R = 0{\cdot}21$ and $R = 0{\cdot}13$ for $0kl$ and $h0l$ reflexions, respectively.

Within experimental error, the molecule is planar, maximum perpendicular distance from mean plane being 0·04 Å. Fig. 1 shows the molecular shape with bond lengths and angles, the corresponding shape of

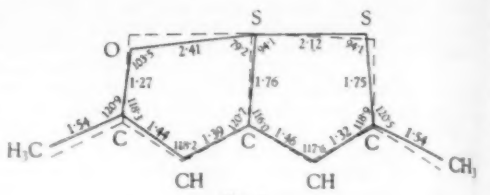


Fig. 1

thio-thiophthene, as obtained after the last refinement, being also drawn for comparison (broken line).

The oxygen–sulphur–sulphur system is seen to be almost linear, with the oxygen atom in the extreme position. These results are in full agreement with the structure proposed in ref. 3, and confirmed in ref. 4 with the aid of nuclear magnetic resonance analysis. Further chemical evidence was recently provided in ref. 5.

A comparison of this structure with the thio-thiophthene system is of great interest. The two molecules have about the same shape, structural configuration and crystal packing: substitution of one sulphur atom with oxygen only causes the electronic arrangement to be slightly different. In fact, we know that each sulphur–sulphur bond in thio-thiophthene may be regarded as made up from both fractional σ and π bonds, the bond orders being 0·707 and 0·439, respectively[6]. The σ and π exchange integrals are, approximately, β and ½β (where β is the carbon–carbon π exchange integral), so that the bond is longer than the single one, even with a bond order sum greater than unity.

Substitution of one sulphur atom by oxygen allows the same electronic interaction to take place only to a much less extent, owing to the different electronegativities of sulphur and oxygen, and to the much smaller overlap between the orbitals of the two atoms. The sulphur–oxygen σ and π overlap integrals for a distance of 2·41 Å. are, in fact, reduced to approximately one-third the values for the sulphur–sulphur interaction in the thio-thiophthene. This reduction must also result in a corresponding increase of sulphur–sulphur overlap integral, in the oxygen–sulphur–sulphur system.

This discussion gives a satisfactory account of the following experimental data: shortening of the sulphur–sulphur bond (2·12 Å.) with respect to thio-thiophthene (the σ bond order is very close to unity); carbon–oxygen distance only slightly longer (1·27 Å.) than the double-bond distance; rather distinct localization of double bonds in the carbon atoms chain; central carbon–sulphur bond length nearly the same as the other.

From Fig. 1 we can also notice in the present structure a reduction of valence angles not only in the right ring, but also in the left one. This means that the abnormal sulphur oxygen length (2·41 Å.), half-way between a single bond and Van der Waals distance, is chiefly to be considered a consequence of the reluctance toward distortion of the carbon atom valence angles. From a geometrical point of view, it may be noted that the carbonylic group is anyway held in the molecular plane by its resonance with the dienic system. We can say, therefore, that the essential features characterizing thio-thiophthene are present in this structure, but to a small extent, so that the actual electronic distribution is best represented by the formula shown in Fig. 2, in which are also indicated, for each bond, the percentage of

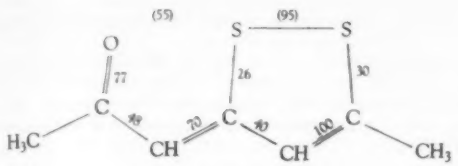


Fig. 2

double bond (or of single bond relatively to Van der Waals radii, for oxygen–sulphur and sulphur–sulphur distances).

For these reasons, the denominations suggested by Prof. Richter, Beilstein Institute, Hamburg (cf. ref. 5), must be accepted as very rational and exact; for 2,5-dimethyl-thio-thiophthene it is:

meribicyclo-epidithio-(2,4)-eptadien-thion(6)

and for 2,5-dimethyl-dithio-furophthene it is:

epidithio-(2,4)-eptadien-on(6)

Further theoretical investigations, of the type performed by Giacometti and Rigatti[6] for thio-thiophthene, are under way, and will give a more exact description. Some other compounds, homologous with thio-thiophthene, with sulphur atoms substituted by possible other group VI elements, are now under examination.

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Hydrogen Bonding in Alkyl Phosphonic and Alkyl Phosphonothionic Acids

In a recent series of papers[1], Peppard *et al.* have examined alkyl and aryl phosphoric and phosphonic acids and their esters. As a result of cryoscopic and infra-red measurements, they have concluded that, except in acetic acid solution, organophosphorus acids are dimeric, or polymeric, depending on the solvent, and that there is no evidence of the monomer in dilute solutions (M/1,000) in carbon tetrachloride. They conclude that the hydrogen bonding in these acids is stronger than that in carboxylic acids. These conclusions are in agreement with those reached by earlier workers[2–5], who all report the bonding to be unaffected by dilution in non-polar solvents. In view of these findings, it has been suggested[3,6] that the hydrogen bonding may be intramolecular.

Examination of more dilute solutions of ethyl methylphosphonic and ethyl methylphosphonothionic acids has shown that, if the dilution is great enough, these hydrogen bonds can be broken, and that the bonding is therefore inter- and not intra-molecular.

Using carefully dried carbon tetrachloride as the solvent, path-lengths of up to 10 cm. and double-beam compensation of solvent absorption, the results shown in Figs. 1 and 2 were obtained. With ethyl methylphosphonothionic acid (Fig. 1), the initial bonded —OH absorption band at 3·27μ (3,058 cm.$^{-1}$) decreases in intensity, relative to the C—H absorption band at 3·4μ (2,940 cm.$^{-1}$), as the concentration of the solution decreases, and is replaced by a new absorption band at 2·78μ (3,600 cm.$^{-1}$). In addition, a band at 4·35μ (2,300 cm.$^{-1}$) progressively decreases in intensity and is replaced by a band at 4·65μ (2,150 cm.$^{-1}$).

In the case of ethyl methylphosphonic acid, the evidence is not so complete owing to experimental limitations. No indication of breaking of hydrogen bonds is obtained in solutions more concentrated than M/3,000. Comparing the spectrum of a 1-cm. path-length of this concentration with that of a 10-cm. path-length of M/30,000 (Fig. 2) shows that the absorption band at 3·8μ (2,630 cm.$^{-1}$) has decreased in intensity relative to the C—H absorption at 3·4μ (2,940 cm.$^{-1}$) and that a new band is appearing at 3·1μ (3,230 cm.$^{-1}$). It was not possible to investigate this problem further as the spectrophotometer would neither accommodate a longer absorption cell nor produce reliable spectra from more dilute solutions over the same absorption path. It might be possible, however, to continue the observations using means such as electronic scale expansion. The detection of a change in the intensity of the bonded OH absorption band, together with the appearance of a band at higher frequency, shows that the hydrogen

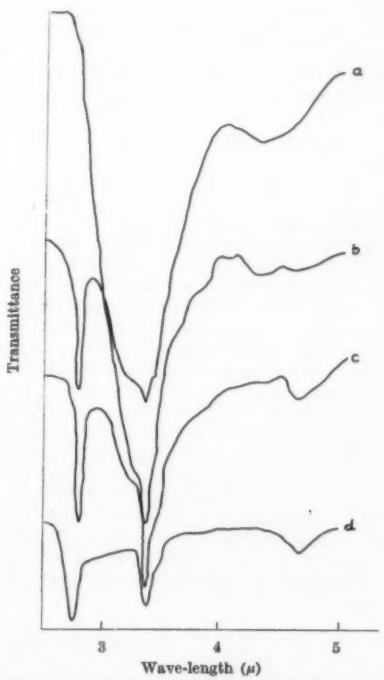


Fig. 1. Spectra of ethyl methylphosphonothionic acid. (*a*) Capillary film, undiluted: (*b*) M/350 in carbon tetrachloride, 1 cm.; (*c*) M/1,750 in carbon tetrachloride, 5 cm.; (*d*) M/3,500 in carbon tetrachloride, 5 cm.

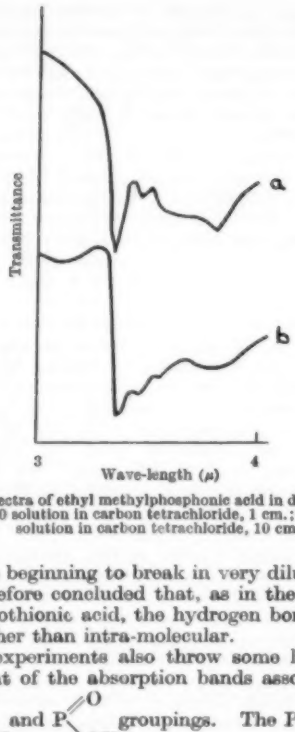
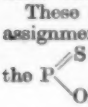
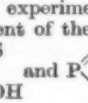
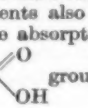
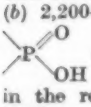
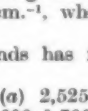
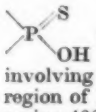


Fig. 2. Spectra of ethyl methylphosphonic acid in dilute solution. (*a*) *M*/3,000 solution in carbon tetrachloride, 1 cm.; (*b*) *M*/30,000 solution in carbon tetrachloride, 10 cm.

bonds are beginning to break in very dilute solution. It is therefore concluded that, as in the case of the phosphonothionic acid, the hydrogen bonds must be inter- rather than intra-molecular.

These experiments also throw some light on the assignment of the absorption bands associated with the  and  groupings. The  group in compounds is characterized by absorption bands in the regions: (*a*) 3,000–3,100 cm.$^{-1}$ and (*b*) 2,200–2,360 cm.$^{-1}$, whereas the same group in  compounds has four characteristic bands in the regions: (*a*) 2,525–2,725 cm.$^{-1}$; (*b*) 2,150–2,350 cm.$^{-1}$; (*c*) 1,600–1,700 cm.$^{-1}$; (*d*) 480–530 cm.$^{-1}$.

As bands (*a*) and (*b*) occur in both types, these must be vibrations associated solely with the P—O—H vibrations, band (*a*) being the O—H valency vibration. In view of the movement of band (*b*) to lower frequencies when the hydrogen bonds are broken, this band is assigned to a combination band involving the OH deformation vibration. Observations on deuteration, which will be reported in more detail elsewhere, have indicated that the O—H deformation vibration in P—O—H groups is in the vicinity of 1,250 cm.$^{-1}$. This is contrary to the assignments for this band given by Bellamy[2] and Corbridge[7], but in agreement with those of Ryskin and Stavitskaya[8]. The P—O—(H) vibration is found in the range 910–1,030 cm.$^{-1}$ (ref. 6) and the combination of the P—O—(H) vibration with the O—H deformation vibration would then result in a frequency in the range ascribed to band (*b*), which is therefore assigned to a combination of these vibrations.

Band (*c*) in  compounds has been assigned[2,6] to the O—H deformation vibration. In the light of evidence from deuteration this assignment is no longer valid. As this band does not appear in  compounds, it may be a combination band involving the P=O vibration. As this occurs in the region of 1,200 cm.$^{-1}$, this implies a frequency in the region 400–500 cm.$^{-1}$ for the other component. Band (*c*) is therefore tentatively assigned to a combination of the P=O valency vibration and of band (*d*), which is otherwise unassigned.

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Synthesis of the Toxic Principle of *Dichapetalum toxicarium* (18-Fluoro-*cis*-9-Octadecenoic Acid)

Dichapetalum toxicarium (*Chailletia toxicaria*, Don), a shrub occurring in Sierra Leone, produces a hard and woody fruit which is extremely toxic to warm-blooded animals. The pharmacological, medical, and historical aspects of this plant have recently been reviewed[1]. Peters and colleagues have concluded[2], on the basis of nuclear magnetic resonance, infra-red spectroscopy and ozonolysis, that the toxic principle is 18-fluoro-*cis*-9-octadecenoic acid (ω-fluoro-oleic acid), $F(CH_2)_8CH{=}CH(CH_2)_7COOH$. It was in order to confirm this conclusion that the following synthesis of ω-fluoro-oleic acid was undertaken:

$$F(CH_2)_8Br + NaC{\equiv}CH \rightarrow F(CH_2)_8C{\equiv}CH + I(CH_2)_7Cl \rightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7Cl + NaCN \rightarrow F(CH_2)_8C{\equiv}C(CH_2)_7CN \rightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7CONH_2 \rightarrow F(CH_2)_8C{\equiv}C(CH_2)_7COOH \rightarrow$$
$$F(CH_2)_8CH{=}CH(CH_2)_7COOH\ (cis)$$

Using *N*,*N*-dimethylformamide and xylene as solvents, 8-fluoro-octyl bromide[3] was converted to 10-fluoro-1-decyne in 60 per cent yield, b.p. 81–82° (10 mm.), n_D^{25} 1·4250, d_4^{20} 0·877 (found: C, 76·48; H, 11·02. $C_{10}H_{17}F$ requires: C, 76·87; H, 10·97 per cent). Previous work[4] had indicated that the ω-fluoro-1-alkynes, in the presence of reactants such as sodamide and Grignard reagents, tended to lose fluorine rather than form the expected acetylenic organometallic derivative; however, by using metallic lithium in liquid ammonia, 10-fluoro-1-decyne formed 1-chloro-17-fluoro-8-heptadecyne in 89 per cent yield, b.p. 137° (0·25 mm.), n_D^{25} 1·4610, d_4^{20} 0·969 (found: C, 70·56; H, 10·38; Cl, 12·42. $C_{17}H_{32}ClF$ requires: C, 70·68; H, 10·47; Cl, 12·28 per cent). Reaction of this last compound with sodium cyanide in dimethyl sulphoxide gave the corresponding nitrile in 93·5 per cent yield, b.p. 139° (0·025 mm.), n_D^{25} 1·4578 (found: C, 77·29; H, 10·77; N, 4·79.

$C_{18}H_{30}FN$ requires: C, 77·36; H, 10·82; N, 5·01 per cent).

Preliminary work using 15-cyano-1-fluoro-7-pentadecyne had indicated the difficulty of hydrolysing this type of nitrile, because the triple bond is susceptible to acidic reagents and the fluorine to vigorous alkaline treatment. The required ω-fluorostearolic acid was ultimately obtained in 73 per cent yield by treatment of 1-cyano-17-fluoro-8-heptadecyne with hydrogen peroxide and alkali followed by hydrolysis of the resultant amide with alcoholic potassium hydroxide, m.p. 52–53° from aqueous methanol (found: C, 72·50; H, 10·28. $C_{18}H_{31}FO_2$ requires: C, 72·31; H, 10·47 per cent). Stereospecific partial hydrogenation of this fluoroacetylenic acid using Lindlar catalyst gave a 99 per cent yield of ω-fluoro-oleic acid, recrystallized from 30–60° petroleum ether at 2° (found: C, 71·92; H, 11·21; F, 6·16. $C_{18}H_{33}FO_2$ requires: C, 71·95; H, 11·07; F, 6·32 per cent). The overall yield from 8-fluoro-octyl bromide was 36 per cent. The physical properties of this acid are shown in Table 1 and are compared with those of a sample of the naturally occurring acid provided by Peters. Hydrogenation of the synthetic ω-fluoro-oleic acid using platinum and hydrogen formed ω-fluorostearic acid, m.p. 77–78° from methanol; mixed with authentic ω-fluorostearic acid[5], m.p. 76–77°.

Table 1

PROPERTIES OF NATURAL AND SYNTHETIC ω-FLUORO-OLEIC ACID

		Natural	Synthetic	Interpretation
Melting point		12·4–13·5°	15·8–16·8°	
n_D^{25}		1·4616	1·4598	
Infra-red (cm.$^{-1}$)*		3,007	3,005	CH stretching of CHR=CHR′ (*cis*)
		1,710	1,711	C=O stretching of COOH
		1,413	1,412	CH in-plane deformation of CHR=CHR′ (*cis*)
		1,048	1,046	C—F stretching
		1,012	1,015	C—F stretching
		726	726	CH out-of-plane deformation of CHR=CHR′ (*cis*)
Nuclear magnetic resonance (c./s.)†	ν‡	258	259	FCH_2-
	J_{HF}	47	47	FCH_2-
	J_{HH}§	6	6	FCH_2-
	ν‡	317	316	—CH=CH—
	J_{HH}§	5	5	—CH=CH—

* Determined using a Beckman *IR*-7 infra-red spectrophotometer; the absence of a band at 980–960 cm.$^{-1}$ indicates the *cis* isomer; elaidic acid showed a strong band at 970 cm.$^{-1}$ resulting from CH out-of-plane deformation of CHR=CHR′ (*trans*).
† Determined using a Varian 60 Mc./sec. *V*-4302*B* spectrometer.
‡ c./s. from tetramethylsilane.
§ Spin–spin interaction with adjacent methylene group.

The proton resonance spectral data are listed in Table 1. The ω-CH_2 group appeared as a doublet of triplets centred at 258 c./s. for the natural material and at 259 c./s. for the synthetic acid; the splitting is due to spin–spin interaction with the terminal fluorine and the adjacent methylene group. The coupling constants were the same in each case. The olefinic protons absorbed at 317 c./s. and 316 c./s. for the two samples, again with identical coupling constants; the olefinic protons in a sample of oleic acid also gave exactly the same results (ν = 316 c./s.; J = 5 c./s.). The results determined for the natural product are in good agreement with those previously reported[5].

There can thus be little doubt that the toxic principle of *Dichapetalum toxicarium* is indeed ω-fluoro-oleic acid. This acid is only the second known naturally occurring organic fluorine compound, the first being fluoroacetic acid. It is not improbable that there is some biogenetic relationship between the two compounds. Further work on this and other ω-fluoro unsaturated acids is in progress.

We thank Sir Rudolph Peters for kindly providing us with a sample of the naturally occurring acid, Allied Chemical Corporation, General Chemical Division, Morristown, N.J., for financial assistance, and Dr. J. B. Stothers of this Department for help with the nuclear magnetic resonance spectra.

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Effect of Strong Electrical Fields on the Boiling Points of some Alcohols

Katti and Chaudhri[1] have published a set of measurements on the effect of electrical fields on the boiling points of methanol, ethanol, and isopropanol. This is an effect which can be calculated from the first principles of thermodynamics.

A boiling liquid in an electrical field does both electrical and pressure-volume work; the conservation of energy equation is $dU = TdS - PdV + EdP'$, where P is the pressure, P' the polarization and E the electric field. Hence the chemical potential of the liquid may be written as:

$$d\mu_1 = -s_1 dT + v_1 dP - p_1 dE$$

where small italics stand for gram molecular quantities. The condition of phase equilibrium is $d\mu_1 = d\mu_g$, hence $(dT/dE)_P = -\Delta p_{1' \to g} / \Delta s_{1 \to g}$. The equation is exactly analogous to the Claperon equation.

For such liquids as methanol, $p' = (\varepsilon - 1)vE$, so that:

$$\frac{dT}{T} = \frac{(\varepsilon_1 - 1)v_1 - (\varepsilon_g - 1)v_g}{\Delta h} EdE$$

If the electrical work stored in the liquid is small compared with the heat of vaporization at zero field, and the change in boiling points is so small that one can ignore changes in the dielectric constants of liquid and vapour, then this equation may be integrated. Approximating $\ln T/T_0$ as $\Delta T/T_0$, we find that:

$$\Delta T = T_0 \frac{(\varepsilon_1 - 1)v_1 - (\varepsilon_g - 1)v_g}{2\Delta h} E^2$$

This equation is valid for a system in which all the material, liquid and vapour, remains within the field. If experiments are done in a constant-volume container (as were Katti and Chaudhri's), a term must be added to the conservation of energy equation to account for the work done in removing vapour from the field. This has the effect of changing v_g to v_1. Since $\varepsilon_g - 1$ is very small compared to $\varepsilon_1 - 1$, this correction is not important, even though the molar volume of the gas is much greater than that of the liquid.

It should be noted that Katti and Chaudhri used an a.c. field. They did not give the frequency, but it was presumably low enough for the dielectric constants to be approximately equal to their d.c. values and high enough for their Beckmann thermometer to

respond to the average temperature. In this case one can calculate the expected change in temperature, taking E as its root mean square value.

Since $\Delta T = C E^2$, where C is a combination of the molecular constants, and using standard values[2] one finds that C in M.K.S. units equals 5·3, 5·5 and 5·7 × 10^{-17} for methanol, ethanol, and isopropanol respectively. Hence, for example, methanol at 5 kV./cm. will show a rise of boiling point of 1·3 × 10^{-5} deg. C. At 5 kV./cm. Katti and Chaudhri observed boiling point depressions of 2·0, 0·7, and 0·4 deg. C. for methanol, ethanol, and isopropanol, respectively, in complete disagreement with theory.

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Since the publication of our communication in *Nature*, several attempts have been made to explain this phenomenon and to calculate the magnitude of the lowering of the boiling points. These attempts naturally deal with the application of thermodynamics to the mechanical effects arising out of the application of strong electrical fields to dielectrics. These models, however, predict very small lowering of the boiling points (of the order of 10^{-5} deg. C. for fields of the order of 5 kV./cm.).

In fact we ourselves were led to this investigation nearly two years ago because of a suggestion by Prof. D. S. Kothari based on the Clapeyron equation with change of pressure replaced by $KE^2/8\pi$. We did not refer to this in our communication because a reference to it was made in an earlier book on physical chemistry and secondly because the sign and the magnitude of the observed changes in the boiling points are not in agreement with this model.

The main purpose of our communication was to point out the unusually large depression of the boiling points of the liquids under the experimental conditions used. More experimental work is clearly necessary, and we hope to report on further results in due course.

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The Optical *F* Absorption Band

In a recent communication[1] a new model for the optical F absorption band was proposed for the alkali metal azides. From a study of irradiation-produced bands in the visible and infra-red region of the absorption spectrum of the azides, it was shown that the anion (N_3^-) was intimately related to the F absorption band and it was suggested that the F band was caused by a 'charge-transfer' complex of the type discussed extensively in the chemical literature, especially by Mulliken[2]. The 'charge-transfer' complex consists of a dative bond being established between one electron donor and an electron acceptor with a concomitant electronic absorption belonging to the complex as a whole.

Table 1. Energy Difference between First Ultra-violet Peak and the *F* Band*

	$h\nu_1 - h\nu_F = C$		$h\nu_1 - h\nu_F = C$
LiF	12·4 −5·0 = 7·4	LiBr	7·2 −2·7 = 4·5
NaF	10·6 −3·6 = 7·0	NaBr	6·78−2·3 = 4·48
KF	9·95−2·7 = 7·25	KBr	6·77−2·0 = 4·77
LiCl	8·8 −3·1 = 5·7	RbBr	6·6 −1·8 = 4·8
NaCl	7·95−2·7 = 5·25	KI	5·8 −1·8 = 4·0
KCl	7·76−2·2 = 5·56	RbI	5·7 −1·6 = 4·1
RbCl	7·5 −2·0 = 5·5		

* $h\nu_1$, energy of first ultra-violet band from Eby, J. E., Teegarden, K. J., and Dutton, D. B., *Phys. Rev.*, **116**, 1099 (1959); $h\nu_F$, energy of the F band from Dekker, A. J., *Solid State Physics* (Prentice Hall, 1959); $h\nu_1$, for LiF estimated from H. C. Kremers, *Indust. and Eng. Chem.*, **32**, 1478 (1940).

For the azides, the following mechanism was proposed for the formation of the 'charge-transfer' complex and the resulting absorption band. Under ultra-violet irradiation an interstitial metal atom is ionized, this metal ion now moves to a position of lower potential energy, that is, to a cation vacancy and as a consequence the equilibrium crystal field is so perturbed (in an unspecified manner) as to set up a 'charge-transfer' complex between that cation and a neighbouring anion. Thus in the proposed model the F absorption band depends on the existence of cation vacancies rather than anion vacancies.

I feel that the phenomena in the halides cannot be essentially different from those in the azides. If one accepts the importance of cation vacancies then several phenomena in the halides can be understood in a straightforward manner. For example, the following experimental facts strongly suggest the importance of the cation vacancy. The electrical conductivity of crystals is decreased by darkening[3]. Plastic strain which enhances conductivity enhances darkening by X-ray irradiation[3]. Divalent cation impurities which increase ionic conductivity enhance colorability by irradiation[3].

The role of the anion in the F band in the halides is not easily demonstrated as in the azides, since there is no infra-red vibration associated with it except for the lattice vibration. However, I suggest that the correlation between the F band and the first ultra-violet absorption band in the halides, first pointed out by Glasner and Tompkins[4], be interpreted in a manner similar to that in the azides. Table 1 lists the difference in energy between the first ultra-violet absorption band in uncoloured crystals and the F band produced in the crystals. It can be seen that the energy difference is a constant for any particular anion. It is generally accepted[5] that the first ultra-violet absorption peak in the halides is caused by the removal of an electron from a halogen ion to a neighbouring metal ion. Our suggested model for the F band is the *partial* removal of an electron to a neighbouring metal ion so that it is not surprising that there exists a relationship between the ultra-violet band and the F band. Further, a colourless electronegative ion with an absorption band in the ultra-violet, under a perturbing influence (the formation of a bond with increasingly greater covalent character), would expect to have an absorption band increase in wave-length proportional to the degree of perturbation[6]. One might expect that any such perturbation would have the greatest effect on the most ionic system. If we use Pauling's function[6], $1-\exp(-\frac{1}{4}(X_a-X_b)^2)$ (where X_a and X_b are the electro-negativities of the atoms in the bond), as a measure of the ionic character for the halides, then the fluorides appear to be most ionic and the iodides least so and the difference in energy between

the ultra-violet band and the *F* band varies in the expected manner. My proposed model for the *F* absorption band is a point defect where just such a phenomenon is occurring.

I cannot justify the imposition of a special site for a cation vacancy which afterwards captures a metal ion except to say that perhaps the ion does not completely enter the vacancy or that there is incomplete relaxation about the vacancy caused by other defects in the neighbourhood.

It has been shown[7] that normal sodium chloride contains about 10^{17} interstitial sodium atoms/c.c. and thus the model yields a plausible mechanism for the formation of *F* centres by low-energy irradiation. The 'charge-transfer' complex also allows one to understand more easily the dichroism observed in *F* centres[8].

Perhaps the most serious drawback to the model is that no explanation is given for the observed electron spin resonance in coloured crystals. I suggest that the electron which is removed from the interstitial metal atom is trapped at another centre giving rise to the electron spin resonance. The optical *F* absorption band and electron spin resonance appear simultaneously but come from two different points in the crystal.

This work was initiated at the Convair Scientific Research Laboratory, San Diego, California.

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BIOCHEMISTRY

Particle Involvement in Fatty Acid Synthesis in Liver and Yeast Systems

THE synthesis of fatty acids from acetate has been shown to occur in particle-free supernatant fractions obtained from a variety of mammalian tissues[1–3]. An examination of the literature[4–7] reveals that such synthesis is significantly increased in the presence of a microsomal fraction. (While the term microsome may be used to describe the particle fraction prepared from liver, it is premature to refer to yeast particles by this name since the cytological fractionation of the yeast cell is less well established. As used here, the term particles refers to the fraction sedimented, after prior removal of the mitochondrial fraction, at 100,000*g* for 45 min. 'Supernatant' refers to the solution obtained after removal of the 100,000*g* pellet.) We have shown, for example, that the addition of rat liver microsomes, in appropriate amounts, results in an increase in the incorporation of acetate carbon into fatty acids many times greater than that observed with the rat liver supernatant fraction alone[8]. Similar observations have been made with a yeast system[9].

Table 1. EFFECTS OF ADDITION OF PARTICLES ON FATTY ACID SYNTHESIS FROM ACETATE IN LIVER AND YEAST SYSTEMS

Supernatant alone	After addition of liver microsomes (ml.)				After addition of yeast particles (ml.)			
	0·025	0·05	0·10	0·30	0·025	0·05	0·10	0·30
Liver, 13·6	25·1	46·2	32·6	7·6	41·1	33·4	23·0	14·2
Yeast, 10·3	13·5	13·2	7·3	3·8	27·3	34·8	29·4	24·9

40 μmoles of potassium phosphate buffer (*p*H 7·5), 15 μmoles of reduced glutathione (K^+ salt), 18 μmoles of $MgCl_2$, 0·25 μmole of $MnCl_2$, 2·5 μmoles of $KHCO_3$, 1·25 μmoles of potassium acetate-1-^{14}C (3×10^5 c.p.m.), 12 μmoles of ATP (K^+ salt), 0·03 μmole of CoA, 0·125 μmole of TPN, and 18·8 μmoles of potassium citrate, all contained in 0·5 ml., were incubated with 0·4 ml. of a particle-free supernatant fraction (11·9 mgm. protein for liver, 8·8 mgm. protein for yeast) plus the amount of particle suspension (in 0·1 *M* phosphate buffer, *p*H 7·5) recorded above (55 mgm. per ml. protein for liver, 67 mgm. per ml. protein for yeast) for 2 hr. at 37° C. with air as the gas phase. The preparation of the liver and yeast fractions in 0·1 *M* phosphate buffer (*p*H 7·5) has been described (refs. 9, 14). The fatty acids were isolated and assayed for carbon-14 activity as described in ref. 15. All values above represent mμmoles of acetate converted to fatty acids per mgm. supernatant protein.

The failure of other workers to observe particle stimulation in mammalian preparations[1,10]—as well as the report that removal of these particles actually increased synthesis[7]—may be explained by our present findings (Table 1), which show that microsomes increase fatty acid synthesis over only a narrow range of concentrations. Indeed, additions of excess amounts of particles reduced synthesis below that observed with the supernatant fraction alone. Since adenosine triphosphate (ATP) is an absolute requirement for fatty acid synthesis from acetate, our findings of high ATPase activity in liver microsomes offers a reasonable explanation for this inhibitory action of the microsomes. The inhibition observed with moderately large amounts of microsomes can be relieved by increasing the ATP concentration in the incubation medium.

Table 1 also shows that yeast particles can be substituted for liver microsomes in the experiments with liver supernatant fractions. Here again, fatty acid synthesis from acetate reached its optimum in the presence of specific amounts of yeast particles, but dropped when those amounts were increased. The addition of liver microsomes to the yeast supernatant fraction failed to augment fatty acid synthesis, but their inhibitory property at high levels was retained. Fatty acid synthesis in the yeast system was less sensitive to large amounts of yeast particles.

The addition of particles also increased the incorporation of the carbon-14 of acetyl-1-^{14}C-coenzyme A (CoA) into fatty acids, but did not affect fatty acid synthesis from malonyl-CoA (Table 2). These findings suggest that particles exerted their effect before the formation of malonyl-CoA in both systems. Evidence that this may be the case in the yeast system comes from the observation that yeast particles are rela-

Table 2. EFFECT OF PARTICLES ON INCORPORATION OF THE CARBON-14 OF ACETATE-1-^{14}C, ACETYL-1-^{14}C-CoA AND MALONYL-2-^{14}C-CoA INTO FATTY ACIDS BY RAT LIVER AND YEAST PREPARATIONS

Labelled substrate	Percentage of carbon-14 incorporated into fatty acids			
	Rat liver		Yeast	
	Supernatant alone	Supernatant + microsomes	Supernatant alone	Supernatant + particles
Acetate-1-^{14}C	5·9	32·3	3·7	23·2
Acetyl-1-^{14}C-CoA	6·1	24·6	4·1	17·1
Malonyl-2-^{14}C-CoA	44·0	51·6	38·5	46·2

60 μmoles of glycylglycine-KOH buffer (*p*H 7·5), 15 μmoles reduced glutathione (K^+ salt), 18 μmoles of $MgCl_2$, 0·25 μmole of $MnCl_2$, 2·5 μmoles of $KHCO_3$, 12 μmoles ATP (K^+ salt), 0·125 μmole of TPN, 18·8 μmoles of potassium citrate and either (*a*) 0·12 μmole of potassium acetate-1-^{14}C ($4{\cdot}5 \times 10^5$ c.p.m.) plus 0·12 μmole of CoA or (*b*) 0·12 μmole of acetyl-1-^{14}C-CoA ($9{\cdot}4 \times 10^5$ c.p.m.) or (*c*) 0·12 μmole of malonyl-2-^{14}C-CoA ($2{\cdot}3 \times 10^5$ c.p.m.) plus 0·02 μmole of acetyl-CoA, all contained in 0·5 ml., were incubated with 0·4 ml. of particle-free supernatant fraction (7·8 mgm. protein for liver and yeast) and 0·1 ml. of particle suspension (2·1 mgm. protein for liver and 5·4 mgm. protein for yeast), as described in Table 1.

Table 3. Incorporation of the Carbon-14 of Acetate-1-^{14}C, Acetyl-1-^{14}C-CoA and Malonyl-2-^{14}C-CoA into Fatty Acids by Rat Liver and Yeast Particles Incubated Alone

Labelled substrate	Percentage of carbon-14 incorporated into fatty acids	
	Liver microsomes	Yeast particles
Acetate-1-^{14}C	0·2	20·3
Acetyl-1-^{14}C-CoA	0·3	14·7
Malonyl-2-^{14}C-CoA	29·0	15·8

60 μmoles of glycylglycine-KOH buffer (*p*H 7·5), 15 μmoles of reduced glutathione (K^+ salt), 18 μmoles of $MgCl_2$, 0·25 μmole of $MnCl_2$, 2·5 μmoles of $KHCO_3$, 12 μmoles of ATP (K^+ salt), 1 μmole of TPNH, and either (*a*) 0·12 μmole of potassium acetate-1-^{14}C ($4·5 \times 10^5$ c.p.m.) plus 0·12 μmole of CoA or (*b*) 0·12 μmole of acetyl-1-^{14}C-CoA ($0·4 \times 10^4$ c.p.m.) or (*c*) 0·12 μmole of malonyl-2-^{14}C-CoA ($2·3 \times 10^5$ c.p.m.) plus 0·02 μmole of acetyl-CoA, all contained in 0·5 ml., were incubated with 0·1 ml. of particle suspension (2·1 mgm. protein for liver and 5·4 mgm. protein for yeast), as described in Table 1.

tively rich in acetyl-CoA carboxylase activity[11]. However, the results reported here indicate that this explanation is not tenable for the liver system.

Particles from liver and yeast were incubated with acetate, acetyl-CoA, or malonyl-CoA, under the conditions shown in Table 3. Liver particles, by themselves, incorporated into fatty acids appreciable amounts of the carbon-14 of malonyl-2-^{14}C-CoA, but not of acetate-1-^{14}C or acetyl-1-^{14}C-CoA. Under identical conditions, yeast particles converted significant amounts of all three substrates to fatty acids. That yeast particles have an enzyme system capable of the complete conversion of acetate to fatty acids receives support from our observation that they contain acetokinase activity equivalent, on a protein basis, to that found in the supernatant fraction (Klein, H. P., and Den, H., unpublished observations). Liver particles, on the other hand, presumably lack acetyl-CoA carboxylase activity, and may be devoid of acetokinase activity. With malonyl-CoA as substrate, if no added co-factor is rate limiting, an additive effect would be expected when the two fractions of each system are combined. But this was not observed (Table 2). The relation of this fatty acid-synthesizing system in the particles to fatty acid synthesis in the system composed of the supernatant fraction plus particles remains to be elucidated.

Although the increase in fatty acid synthesis from acetate and from acetyl-CoA induced by liver microsomes is not due to their ability to convert acetyl-CoA and bicarbonate to malonyl-CoA, the possibility exists that malonyl-CoA is supplied through an interaction between the particles and the supernatant fraction. It is conceivable that some compound in the system may donate a carboxyl group to acetyl-CoA without passing through a bicarbonate pool (cf. Swick and Wood[12]). We have reported[3] that, while glucose-6-phosphate or malate will produce adequate amounts of reduced triphosphopyridine nucleotide (TPNH) for fatty acid synthesis from acetate in mammalian systems, these compounds do not stimulate fatty acid synthesis as effectively as do citrate, isocitrate, and aconitate. These tricarboxylic acids, which yield amounts of TPNH comparable with those formed from malate or glucose-6-phosphate, are distinctly superior in their capacity to augment fatty acid synthesis from acetate or acetyl-CoA. (The addition of liver microsomes to the supernatant fraction oxidizing citrate-6-^{14}C will increase the rate and level of $^{14}CO_2$ production.) It is therefore reasonable to infer that the tertiary carboxyl group of citrate may be involved in a transcarboxylation reaction with acetyl-CoA leading to the formation of malonyl-CoA. The supernatant fraction, containing isocitric dehydrogenase and aconitase, would initiate this reaction, which would then be completed by particles through a transcarboxylase reaction. Numa *et al.*[13] were unable to demonstrate transcarboxylase activity in rat liver preparations, but their examination of transcarboxylase activity was confined to the particle-free supernatant fraction only.

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Comparative Effects of 2,4-Dinitrophenol on the Actomyosin Adenosine Triphosphatase from Fresh, Frozen and Freeze-dried Beef

In our work on biochemical alterations in beef consequent upon freeze-drying the evidence obtained so far indicates that the changes are probably subtle. Previously[1] we reported that there is little change between the salt solubility of frozen and freeze-dried beef and that only small differences occurred in the amount of sedimentable actomyosin. No consistent difference appeared in the adenosine triphosphatase (ATPase) activity of actomyosin extracts from these materials, and the electrophoretic patterns shown by sarcoplasmic protein extracts were almost identical for frozen and freeze-dried beef, under the conditions used. With contractile protein extracts there was noticeable alteration in the freeze-dried pattern indicating denaturation.

In present work reported here, designed to detect ageing changes in beef, I have compared the stimulatory effects of 2,4-dinitrophenol (DNP) on actomyosin ATPase preparations from fresh, frozen and freeze-dried beef. While there were no demonstrable changes ascribable to ageing, I observed a consistently greater stimulation by DNP of the actomyosin ATPase from fresh beef than from frozen and freeze-dried beef.

Actomyosin extracts were prepared in two ways from semitendinosus and longissimus dorsi muscles. Precipitated actomyosin was prepared by the conventional technique of extraction with 0·53 ionic strength buffer *p*H 8·2 and dilution to ionic strength 0·08. Actomyosin obtained indirectly was prepared as previously described[1]. The only procedural change was the substitution of a Virtis blender (1½ min.) for the Waring blender.

Beef carcasses (hindquarters or short hips right and left sides) were received on the dates shown in Table 1. Muscle designated as 'not aged' was excised within 18 hr. of receipt. From this, samples labelled 'fresh' were taken for immediate analysis. The remainder was frozen in air at −29° C. for periods of 24–48 hr. The frozen muscle was cut into slices 3/4 in. thick. One portion was kept frozen and the other freeze-dried by radiant heating at a chamber pressure between 0·4 and 0·5 mm. mercury[2]. Analyses of the frozen samples were begun during this 48-hr. period. Freeze-dried samples were vacuum-packed immediately on removal from the drying chamber, and stored at − 29° C. Analyses of the latter were always made within 2 weeks of freeze-drying.

Samples designated as 'aged' were taken from the opposite hind limb, which was hung (aged) for 3 weeks at + 4° C. At the end of the ageing period the muscles were excised and treated in the same manner as the unaged samples.

The ATPase activities of the extracts were determined at 30° C. in a manner similar to that described previously[1], the final concentration of reactants being: calcium chloride 0·005 *M*, DNP 0·004 *M*, ATP 0·0025 *M*, potassium chloride 0·10 *M*, *tris*-(hydroxymethylaminomethane) 0·05 *M*, *p*H 8·1. The concentration of enzyme giving a linear reaction-rate for the 10-min. period was found to be between 0·200 and 0·300 mgm. nitrogen.

The results are shown in Table 1.

Table 1. Comparison of DNP Stimulation of Actomyosin ATPase from Fresh, Frozen, Freeze-dried Beef

	Precipitated actomyosin			Indirect	
	Without DNP	Percentage stimulation with DNP		Without DNP	Percentage stimulation with DNP
S.T. aged 29/3/60			S.T. aged 7/1/60		
Fresh	35·5	104·2	Fresh	60·2	62·0
Frozen	57·2	37·2	Frozen	65·2	45·7
F.D.	40·7	9·8	F.D.	44·6	41·2
S.T. not aged 29/3/60			S.T. not aged 7/1/60		
Fresh	39·9	71·0	Fresh	54·0	53·2
Frozen	58·4	7·0	Frozen	47·6	25·6
F.D.	43·1	55·0	F.D.	43·1	35·0
S.T. aged 7/1/60			S.T. aged 29/3/60		
Fresh	48·7	53·6	Fresh	54·1	61·2
Frozen	64·1	14·2	Frozen	45·1	7·5
F.D.	61·9	3·3	F.D.	55·6	1·6
S.T. aged 16/11/59			S.T. not aged 29/3/60		
Fresh	36·5	41·0	Fresh	54·0	53·2
Frozen	32·0	32·2	Frozen	47·7	30·2
F.D.	52·1	15·5	F.D.	43·1	35·0
L/D aged 29/3/60			L/D aged 29/3/60		
Fresh	44·2	57·5	Fresh	46·1	74·0
Frozen	53·1	5·8	Frozen	52·3	20·2
			L/D not aged 29/3/60		
			Fresh	41·2	126·5
			Frozen	55·5	11·5

Activities expressed in μgm. P/min./mgm. N.
S.T., Semitendinosus muscle; L/D, longissimus dorsi muscle; F.D., freeze-dried.

It is well known that DNP stimulates the calcium-activated ATPase of myosin and actomyosin[3–5]. However, no previous report appears to be available concerning the effect of DNP on actomyosin from post-rigor muscle. The mechanism by which stimulation is achieved is not agreed upon. At temperatures above 16° C., DNP also stimulates the cytidine triphosphatase (CTPase) activity of myosin but inhibits the inosine and guanosine triphosphatase (ITPase, GTPase) activity[5,7]. It has been postulated that retardation of hydrolysis of the former two enzymes results from the interaction of —SH or other groups in the enzyme and the 6-NH_2 group common to both adenine and cytosine. This retardation is relieved or removed by the action of DNP on the rate-retarding group of the protein[6–8]. There is no such retardation with the 6-OH base present, for example inosine, and DNP does not stimulate hydrolysis.

Gilmour and Griffiths[5] have suggested that since myosin aggregates at 25° C., there is consequent masking of the active centres. At 0° C. there is no masking and no stimulation by DNP. At the higher temperature, DNP is thought to achieve its effect by splitting the polymer and restoring the enzyme to the state in which it exists at 0° C.

The finding of Perry and Chappell[4] that stimulation of myosin ATPase is depressed by an increasing actin/myosin ratio in synthetically prepared actomyosins also bears on the interpretation of these results. The mechanism by which actin can reverse the DNP effect is not understood, but it is presumed that actin can alter the nature or sequence of events at the active centres of myosin.

In the light of the foregoing, the results presented in Table 1 may be interpreted in either of two ways. The depressed stimulation shown by the frozen and freeze-dried samples could be due to unmasking of the active centres during freezing and drying. This would imply the existence of some depolymerizing process as a result of freezing or drying. It is highly unlikely that depolymerization occurs[1]. Moreover, the DNP–ATPase activities of the pellet from actomyosin fractionated at high speed (Cole, unpublished results) show no consistent differences from those of the supernatant liquid. If particle-size affected the DNP–ATPase this would be reflected in greater stimulation of pellet enzyme material.

A second and more logical interpretation of the results reported above can be based on a changed or changing active myosin/actin ratio. A preferential denaturation of myosin in the actomyosin complex would decrease this ratio and thus decrease the stimulatory effect of DNP.

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Formation of Auxin-bound Proteins

THE occurrence of auxin–protein complexes has been recognized for a long time, but very little is known about the mechanism of the binding process. According to Siegel and Galston[1] energy for the coupling of auxin to protein is supplied by adenosine triphosphate, and the process can be inhibited by several metabolic inhibitors. Galston *et al.*[2,3] have observed, using indole-3-acetic acid (IAA) labelled with carbon-14, that auxin is not bound appreciably to any of the cell organelles but that the particle-free supernatant contains macro-molecules to which auxin is bound. Masuda[4] has recently put forward the suggestion that IAA may render ribonucleic acid (RNA) separate from ribonucleoprotein by becoming complexed with the protein moiety. During the course of an investigation on the binding of auxin to protein in growing tissues it was observed that several amino-acids stimulated the binding process. This communication summarizes some of the observations made concerning the inter-relationship between the binding process and protein synthesis.

The auxin used was naphthalene acetic acid-1-^{14}C (NAA-^{14}C) obtained from Tracerlab Inc., Waltham, Mass., United States. The specific activity of this preparation was rather low (6·7 μc./mgm.); in the experiments described here, concentrations lower than 5×10^{-4} *M* could not be used. To study the effect of amino-acids on the binding of NAA-^{14}C to protein, pea-internode sections (var. Duke of Albany) were allowed to metabolize different amino-acids in phosphate buffer of *p*H 6·0 in the presence of NAA-^{14}C, and the proteins precipitated by trichloracetic acid (TCA). It can be seen from Table 1 that all the amino-acids used promoted the binding of NAA-^{14}C to protein, and the stimulation was particularly noteworthy in the case of aspartic acid. With aspartic acid, glutamic acid and leucine, incorporation of carbon-14 into the TCA-precipitable proteins was higher at 10^{-3} *M* than at 10^{-6} *M*. It is not known, however, whether these amino-acids or the auxin-amino-acid conjugates—if such conjugates were formed in the present case—participated in the formation of the auxin-bound protein.

Table 1. EFFECT OF AMINO-ACIDS ON THE BINDING OF NAA-^{14}C TO THE 'PROTEIN' OF PEA (VAR. DUKE OF ALBANY) INTERNODES

Treatment	Per cent incorporation of carbon-14 after 3 hr.
Control	100
Aspartic acid 10^{-6} *M*	215
Aspartic acid 10^{-3} *M*	333
Glutamic acid 10^{-6} *M*	105
Glutamic acid 10^{-3} *M*	243
Serine 10^{-6} *M*	115
Serine 10^{-3} *M*	129
Leucine 10^{-6} *M*	180
Leucine 10^{-3} *M*	214
Alanine 10^{-6} *M*	158
Alanine 10^{-3} *M*	158
Glycine 10^{-6} *M*	158
Glycine 10^{-3} *M*	154

If new protein is formed, it may be expected that chloramphenicol—which has been reported to be an inhibitor of protein synthesis—would inhibit the process of formation of the auxin-bound protein. Accordingly, internode sections were incubated with three different concentrations of chloramphenicol. The results are shown in Fig. 1. It is surprising to note that even at 10^{-3} *M* no inhibition was observed; 10^{-5} *M* chloramphenicol brought about a stimulation. Some inhibition was observed if the NAA-^{14}C was added 1 hr. after pre-incubation with chloramphenicol.

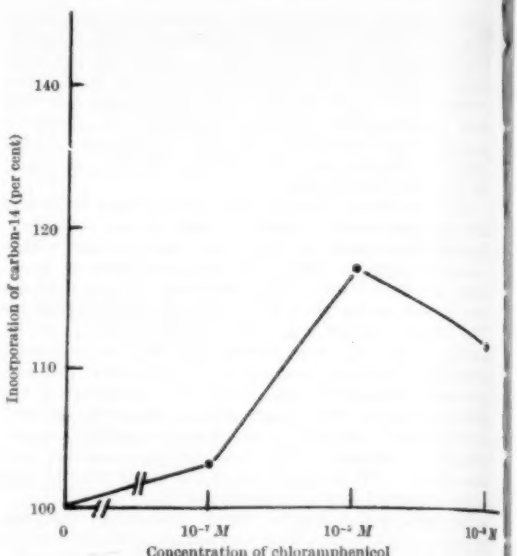

Fig. 1. Effect of chloramphenicol on the binding of NAA-^{14}C to protein of internodes of peas

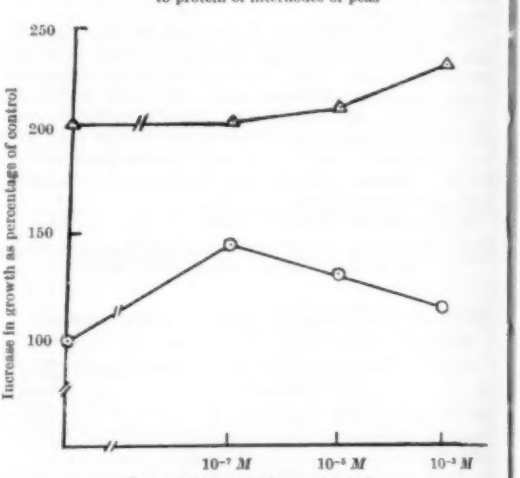

Fig. 2. The effect of different concentrations of chloramphenicol on the growth of *Avena* coleoptiles in presence (△) or absence (○) of 10^{-6} *M* IAA

Since the binding of auxin to protein is usually supposed to be related to the growth process, it was necessary to see whether chloramphenicol inhibited auxin-induced growth. The results are shown in Fig. 2. Chloramphenicol not only fails to inhibit growth, but also has no marked effect on the incorporation of ^{14}C-labelled amino-acids into the proteins. At 10^{-3} *M* some inhibition was observed in the case of glycine-2-^{14}C (Table 2).

In subsequent experiments the effect of ribonuclease (bovine pancreas RNase, Sigma Chemical Co., St. Louis, Mo., U.S.A.) on the binding process was investigated. *Avena* coleoptiles were used, since from the work of Masuda[5] it appears that RNase penetrates coleoptile sections. The coleoptiles were treated with RNase (100 μgm./ml.) for 2·5 hr.,

Table 2. Effect of Concentrations of Chloramphenicol on the Incorporation of Glycine-2-^{14}C and Leucine-1-^{14}C into the 'Protein' of Pea (var. Duke of Albany) Internodes

Amino-acid	Concentration of chloramphenicol	Per cent incorporation of carbon-14 after 3 hr.
Glycine-2-^{14}C (5×10^{-4} *M*)	0	100
	10^{-4} *M*	139
	10^{-3} *M*	84
Leucine-1-^{14}C (5×10^{-4} *M*)	0	100
	10^{-4} *M*	133
	10^{-3} *M*	98

Table 3. Effect of RNase on the Binding of NAA-^{14}C to the 'Protein' of Pea (var. Duke of Albany) Internodes

Treatment	c.p.m./mgm. of 'protein' after 3 hr.
Control	600
RNase (100 μgm./ml.)	809

washed and incubated again for 3 hr. in darkness at 28° C. in the presence of NAA-^{14}C. From Table 3 it is apparent that treatment with RNase has no inhibitory effect. On the other hand, some stimulation was observed. No inhibition was found even when the period of incubation with NAA-^{14}C was reduced to 1 hr.—a period much shorter than that required by the coleoptiles to overcome the inhibitory effect of RNase[4]. The process of binding of auxin to protein, thus, does not appear to be an RNA-controlled process. Whether the stimulation in binding due to RNase treatment is caused by the liberation of nucleotides[5] which help in the binding of auxin to protein, or due to an increased availability of sites for the binding of auxin owing to the separation of RNA from ribonucleoprotein, is not known at present.

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Effect of Indole-3-Acetic Acid (IAA) on Phosphorus Metabolism in the *Avena* Coleoptile

It is generally believed that energy-rich phosphate compounds act as a store-house of energy for different reactions during growth. The auxin-induced stimulation of respiration is presumed to be due to an increased availability of phosphate acceptors due to the rapid utilization of nucleotides during the growth process[1–3]. Rhodes and Ashworth[4] have speculated on the mechanism by which growth substances may be metabolized for the generation of energy-rich phosphate bonds, but an unequivocal demonstration of the stimulation of nucleotide synthesis is not available. Ormrod and Williams[5] and Key *et al.*[6] have recently observed increased phosphorylating activities in plants sprayed with 2,4-dichlorophenoxyacetic acid. Marre and Forti[7] had noted a rapid increase in high-energy phosphate level in auxin-treated pea internode segments during the first 30 min., followed by a decline. The method of estimation of adenosine triphosphate (ATP) adopted by them, which involves the adsorption of adenine nucleotides on charcoal followed by elution with hydrochloric acid, has several limitations when applied to tissue sections. Since numerous metabolic reactions go on in the cell at the same time, and a large number of them concern the participation of nucleotides, particularly reactions mediated by the kinase type of enzyme, and the phosphate residues are transferred to a variety of substrates, estimation of the level of adenine nucleotides at any given time is not the true measure of the total ATP formed during the experimental period. A more correct approach is to estimate the phosphate esterified to organic compounds including the nucleotides. Phosphate labelled with phosphorus-32 may be conveniently used for this purpose and the present communication summarizes the findings of an investigation directed towards this objective.

Five-mm. sections of 4-days old *Avena* coleoptiles (var. *N.P.*1) were incubated with radioactive disodium hydrogen phosphate ($Na_2H^{32}PO_4$) and different concentrations of IAA in *M*/150 phosphate buffer of *p*H 6·0 for 1 and 2 hr. The tissues were extracted with 80 per cent ethanol and the concentrated extract chromatographed two-dimensionally with phenol/water as the first, and butanol/acetic acid/water (4 : 1 : 1) as the second, solvent for 48 hr., or unidimensionally in 69 per cent butyric acid in 0·85 per cent sodium hydroxide, followed by autoradiography with Ilford X-ray films. The sum of the ^{32}P-activities in the radiation spots other than inorganic phosphate was taken as a measure of phosphate-^{32}P esterified. It may be observed from Fig. 1 that with low concentrations of IAA in the experimental solution, esterification of ^{32}P was increased considerably; at 10^{-3} *M*, a concentration which was inhibitory to growth, esterification was also inhibited. The stimulation in esterification

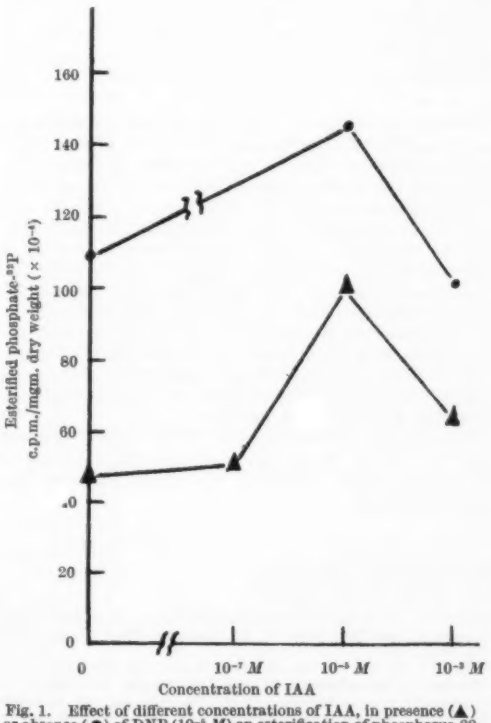

Fig. 1. Effect of different concentrations of IAA, in presence (▲) or absence (●) of DNP (10^{-5} *M*) on esterification of phosphorus-32 (from $Na_2H^{32}PO_4$) in the 80 per cent ethanol-soluble fraction of *Avena* coleoptile sections; experimental period 2 hr.

observed at the end of 1 hr. was greater than that after 2 hr. Similar results were obtained with rice coleoptiles.

When 10^{-5} *M* 2,4-dinitrophenol (DNP), the uncoupling agent of phosphorylation, was included in the experimental solution it was found that DNP itself inhibited the esterification of phosphate-^{32}P by more than 50 per cent. The inhibitory effect was countered by low concentrations of IAA. IAA at 10^{-7} *M* had very little effect, but the higher concentration of 10^{-5} *M* considerably diminished the inhibitory effect due to DNP. IAA at 10^{-3} *M*, which inhibited esterification, failed to oppose the effect of DNP to any great extent.

The effect of IAA and DNP on individual compounds is shown in Table 1. Phosphate-^{32}P was metabolized mainly to hexose phosphates, ATP and ADP, and an unidentified compound designated 'compound *X*' in Table 1. While changes in activity in the sugar phosphates and adenine nucleotides reflected the pattern observed in investigation of phosphate esterification, incorporation of phosphorus-32 into compound *X* increased with increasing concentrations of IAA. DNP completely inhibited its formation; it reappeared only when DNP was combined with 10^{-3} *M* IAA.

Table 1. Effect of IAA and DNP on the Incorporation of Phosphorus-32 from $Na_2H^{32}PO_4$ into the 80 per cent Ethanol-soluble Phosphorylated Compounds of *Avena* Coleoptiles. Specific Activity (c.p.m./mgm. × 10^{-3}) after Inhalation for 2 hr.

Treatment	Hexose phosphate	ADP + ATP	'Compound *X*'
Control	154·6	545·4	75·1
IAA 10^{-5} *M*	269·6	721·8	162·7
IAA 10^{-3} *M*	203·0	365·5	164·7
DNP 10^{-5} *M*	97·1	235·0	0
DNP 10^{-5} *M* + IAA 10^{-7} *M*	89·2	185·0	0
DNP 10^{-5} *M* + IAA 10^{-6} *M*	152·7	322·2	0
DNP 10^{-5} *M* + IAA 10^{-3} *M*	120·8	316·4	26·8

Results obtained in this work reveal an increased incorporation of phosphorus-32 in both the alcohol-insoluble fraction and in the esterified organic compounds in the alcohol-soluble fraction in the presence of low concentrations of IAA which promote the growth of coleoptiles. If the phosphorylase and phosphatase activities of these tissues are not very high, this may be taken to reflect largely, if not entirely, the formation of energy-rich nucleotides as affected by auxins. The inhibition by DNP and its counter-action by IAA provide further evidence in support of the contention that application of auxins leads to metabolic changes resulting in an increased synthesis of energy-rich nucleotides utilized in various reactions involved in the growth process.

Our thanks are due to Dr. D. M. Bose, director, and Dr. P. K. Bose, head of the Department of Chemistry, Bose Institute, for their interest and encouragement.

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Quantitative Aspects of the Re-utilization of Protein-bound Amino-acids *in vivo*

The extent of the re-utilization of protein-bound amino-acids in the formation of new protein has been a subject of interest for many years[1–3]. The main difficulty with some of the work reported in the literature has been that the half-life of the protein into which the re-utilized amino-acid residue was traced was short. Thus, when one injects a labelled soluble protein and determines the uptake of the label into liver or serum proteins (the half-lives of which are a few days in extent) one deals with a situation in which the uptake, transfer and loss of label is rapid and, furthermore, where the 'recipient' protein continually recirculates some of the amino-acid to itself. In these circumstances one is unable to assess reliably the significance or extent of the re-utilization.

In this communication we describe the quantitative re-utilization of amino-acids from serum protein to globin. Globin is a protein which, contained in the red cell, enjoys a life-span of about 55 days in the rat. Thus, over a reasonably short period no globin formed during that interval of time is broken down.

22 hr. after injecting a rat with 1 mc. (about 20 mgm.) of glycine-2-^{14}C, the animal was bled and serum albumin and serum globulin were prepared by methods described in ref. 3. 20 mgm. of either labelled serum albumin or serum globulin containing 65 mμc./mgm. were injected intravenously into recipient rats. Animals were killed 1, 3, 6, 9, 12 or 15 days after the injection and globin was prepared from washed erythrocytes by the method in ref. 4. Dry protein powders[3] of the globin and also of aliquots of the injected serum protein were hydrolysed in 6 *N* hydrochloric acid for 24 hr. and the hydrolysate was then treated with 2,4-dinitrofluorobenzene according to Levy[5]. The dinitrophenyl glycine was separated from the other dinitrophenyl-amino-acids on a 'Celite' column and purified as described in ref. 6. Samples of the injected protein and of the dinitrophenyl glycine from injected protein and from globin were counted using a *D*-47 Nuclear-Chicago flow-gas counter with 'Mylar' window. When sample weights differed from 30 mgm. a self-absorption correction was applied. In addition, the counts obtained for dinitrophenyl glycine samples were recalculated for free glycine.

In preliminary experiments we found that the half-life of serum albumin is 3 days and of serum globulin is 4 days in the Sherman strain rats used in these experiments. Furthermore, it was established that about 31 per cent of the radioactivity of serum albumin or serum globulin is due to glycine when these proteins are prepared as described here and the remainder of the activity is in serine. In experiments to be reported in full elsewhere it was also found that the conversion of labelled serine to labelled glycine, in recipient animals injected with glycine-serine labelled serum proteins, does not materially affect the results of the calculation presented here.

Using the data obtained in the above experiments it is possible to calculate the percentage serum albumin and serum globulin glycine re-utilized in globin synthesis. The percentage of the total glycine required for globin synthesis which has its origin in serum protein glycine can also be determined.

The calculation is based on the counts/min./mgm. of globin glycine found at time *t* after injection; the total serum protein-bound glycine activity injected into the rat; the assumption that 3·4 per cent of the

body-weight corresponds to the total packed red cell volume, that there are 314 mgm. of hæmoglobin/ml. packed cells[7] and that the life-span of red cells is 55 days in the rat[8]. Furthermore, the glycine content of globin is assumed to be 4·8 per cent[9], that of serum globulin 4·3 per cent and that of serum albumin 1·6 per cent[9,10]; the molecular weight of hæmoglobin is taken at 68,000 and that of globin at 65,400 (ref. 11). The sample calculation presented here is one which is based on a rat injected with labelled rat serum globulin and killed 12 days later.

The final calculated results are typical of those obtained in rats injected with serum globulin and killed at any of the times after injection mentioned here.

A sample calculation of the re-utilization of serum globulin glycine in globin biosynthesis is as follows:

(1) Total glycine radioactivity released on breakdown of injected labelled serum globulin from time 0 to time t (t = 12 days): Counts/min. injected × percentage activity in glycine × fraction degraded at time t = 196,500 × 31 per cent × 87·5 per cent = 53,300.

(2) Total mgm. glycine released a day on breakdown of serum globulins: Rat weight (gm.) × ml. serum/gm. body-weight × mgm. serum globulin/ml. × percentage glycine in serum globulin × fraction of serum globulin degraded a day = 283 × 0·034 × 32·2 × 4·3 per cent × 16 per cent = 2·13.

(3) Total mgm. glycine required in globin synthesis a day in this rat: Weight of rat (gm.) × ml. packed red cell volume per gm. body-weight × mgm. hæmoglobin/ml. $\times \frac{\text{M.W. globin}}{\text{M.W. hæmoglobin}}$ × per cent glycine in globin $\times \frac{1}{\text{life span of red cells}} = 283 \times 0{\cdot}034 \times 314 \times \frac{65{,}400}{68{,}000} \times 4{\cdot}8 \text{ per cent} \times \frac{1}{55} = 2{\cdot}54.$

(4) Total radioactivity incorporated into total globin glycine from time 0 to time t (t = 12 days): Counts/min./mgm. globin glycine × total mgm. globin glycine = counts/min./mgm. globin glycine × mgm. glycine required in globin synthesis a day × life-span of globin = 4·38 × 2·54 × 55 = 612.

(5) Percentage serum globulin glycine radioactivity incorporated into globin glycine:

$$\frac{\text{total counts/min. in globin glycine}}{\text{total glycine counts/min. released from serum globulin}} \times 100 = \frac{612}{53{,}300} \times 100 = 1{\cdot}15.$$

(6) Weight of serum globulin glycine incorporated into globin glycine over this 12-day time-period: mgm. serum globulin glycine released per day × days × fraction serum globulin glycine counts/min. incorporated in globin = 2·13 × 12 × 0·0115 = 0·294.

(7) Percentage of total glycine required in globin synthesis which has its origin in serum globulin glycine:

$$\frac{\text{Weight of serum globulin glycine incorporated into globin}}{\text{Total mgm. glycine incorporated into globin in 12 days}} \times 100 = \frac{0{\cdot}294}{2{\cdot}54 \times 12} \times 100 = 0{\cdot}96.$$

Thus about 0·96 per cent of the total glycine required in globin synthesis has its origin in serum globulin and approximately 1·15 per cent of serum globulin glycine is used for globin synthesis. Similar experiments with rats injected with labelled serum albumin indicate that 0·57 per cent of the total glycine required in globin synthesis has its origin in serum albumin and approximately 1 per cent of serum albumin glycine is used for globin synthesis. This contribution by serum proteins of 1·5 per cent of the total glycine required in globin synthesis must be deemed significant in view of the fact that serum proteins constitute only 2 per cent of the rat's total proteins.

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Isolation of Echinochrome *A* from the Spines of the Sea Urchin, *Stomopneustes variolaris* (Lamarck)

I have reported the presence of echinochrome *A* (7-ethyl-2,3,5,6,8-pentahydroxy-1,4-naphthaquinone) in the spines of the sea urchin, *Echinarachnius* (Scaphechinus) *mirabilis*[1] and *Diadema setosum*[2]. Recently it was found that the principal naphthaquinone pigment in the almost black spines of the sea urchin, *Stomopneustes variolaris* (Lamarck) (Japanese name, kuro-uni), which was collected at Shirahama in Wakayama Prefecture, was identical with echinochrome *A*. The isolation and purification of the pigment have been carried out by the identical method used in the case of *Diadema setosum*.

The pure pigment crystallized from dioxane–water in dark red-brown needles and melted at 215°. The yield of the pure material was about 26 mgm. from each 100 gm. of the spines. Absorption maxima were at 256, 340, 466, 489, 525 mμ in chloroform and the percentage of carbon and hydrogen was 53·63 and 3·40 respectively (calc. for $C_{12}H_{10}O_7$: C, 54·14; H, 3·79).

The trimethyl derivative of the pigment was obtained as long, red needles when it was methylated with diazomethane and crystallized from dioxane–water. It melted at 130° (sealed tube) and showed absorption maxima at 249, 323·5, 478, 503, 538 mμ in chloroform. The percentage of carbon and hydrogen was 58·53 and 4·96 respectively (calc. for $C_{12}H_7O_4$-

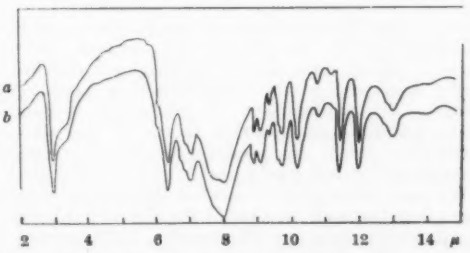

Fig. 1. Infra-red spectra: *a*, free pigment of *Stomopneustes variolaris*; *b*, echinochrome *A* of *Diadema setosum* (potassium bromide)

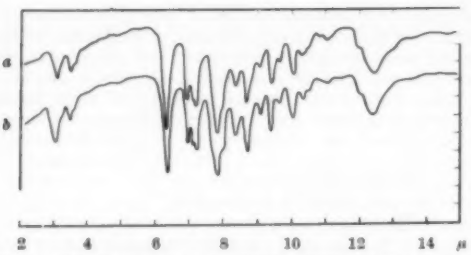

Fig. 2. Infra-red spectra: *a*, trimethyl derivative of the pigment of *Stomopneustes variolaris*; *b*, trimethyl echinochrome *A* of *Diadema setosum* (potassium bromide)

$(OCH_3)_3$: C, 58·35; H, 5·29). It was soluble in aqueous sodium hydroxide giving a blue colour.

The yellow dehydro-derivative having absorption maxima at 257·5, 319, 392 mμ (in aqueous methanol) was obtained when the free pigment was dehydrogenated with the peroxidase–hydrogen peroxide system. The original red pigment was regenerated when the dehydro derivative was treated with hydrogen sulphide.

The colour reactions and the ultra-violet, visible and infra-red absorption spectra of the free pigment and of the trimethyl derivative were in fair agreement with those of authentic specimens of echinochrome *A* and trimethyl echinochrome *A*, respectively. No depression of the melting point was observed when the mixed melting point examination was carried out with authentic specimens of echinochrome *A* and trimethyl echinochrome *A*, respectively.

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PHYSIOLOGY

Inhibitory Phenomena and 'Habituation' at the Neuronal Level

In behavioural habituation, according to Thorpe[1], the animal "learns not to respond to stimuli which tend to be without significance in the life of the animal". It does so by a mechanism which determines a "relatively permanent waning of a response as a result of repeated stimulation". Different authors conceive that the phenomenon of habituation may be correlated with changes in the central nervous system: (*a*) development of inhibitory connexions, in a way analogous to the extinction of a conditioned reflex[2]; (*b*) development of inhibitory influences acting on different synaptic relays of the sensory pathways, which, by producing 'afferent neuronal habituation', would lead to behavioural habituation[3].

We have attempted to analyse the nature of these changes in the snail, in which behavioural habituation was described long ago (Humphrey, 1933, quoted by Thorpe[1]). In electrophysiological investigations with intracellular microelectrodes on the ganglion cells of the snail and other molluscs, Tauc[4,5] has recently described postsynaptic inhibitory potentials, and inhibitory effects of long duration, which might be relevant in an interpretation of the mechanism of habituation.

Our experiments were performed in an isolated nervous system preparation of the land snail (*Helix*). The whole pericesophageal ring of nervous ganglia and commissures, together with the mantle nerves, was cut loose and partially desheathed. It was mounted in a 'Lucite' chamber and covered with Cardot's solution. The mantle nerves were threaded through small holes into a neighbouring chamber, and mounted on bipolar platinum–iridium electrodes and covered with mineral oil. Intracellular electrical recording was carried out with conventional glass micropipettes filled with 2·5–3 *M* potassium chloride.

In the course of exploratory recording of the electrical activity of different cells in the parietal ganglia, we concentrated our observations on a group of two or three big cells (150–225μ in diameter) at the medial side of the right parietal ganglion, just left of the root of the internal right mantle nerve. We selected these cells because of their size, easy recognition, and stability of response (a couple of hours).

When a micropipette penetrates the cell membrane, a resting potential of 40–60 mV. is recorded, with an occasional burst of spikes. After some minutes of impalement, these neurones exhibit a low-frequency discharge of impulses, with slow and irregular changes in frequency, or with alternating periods of activity and silence. We speak of this as 'spontaneous' activity not prejudging if it is due to random synaptic bombardment or autorrhythmic activity generated in the impaled cell itself. Not only full-sized spike potentials (with an overshoot of 20–40 mV.) but also abortive or incipient spikes, and slower or faster oscillations of the membrane potential, in a depolarizing or hyperpolarizing direction, may be recorded.

If the ipsilateral mantle nerve is stimulated with electrical pulses at rather low frequencies (1–5 sec.$^{-1}$), each stimulus may at the beginning drive a full-sized spike potential in the neurone (Fig. 1). After a certain number of stimuli, both the driven responses, and the 'spontaneous' impulses as well, are blocked and replaced by an oscillating type of hyperpolarizing activity, which either builds up gradually during stimulation or appears abruptly after some stimuli. In many cases, with adequate amplification and time base, each afferent impulse can be seen to be followed by a hyperpolarizing potential with quite a regular latency. These hyperpolarizing effects have been

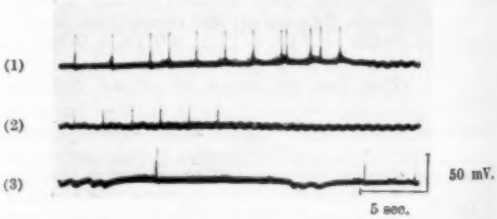

Fig. 1. Electrical activity of snail ganglion cell (continuous record except for 18 sec. cut between (2) and (3)). (1) Neurone discharges 'spontaneously'. Stimulation of ipsilateral mantle nerve at a frequency of 5/sec. 'Driven' spikes, preceded by slight positive potentials, can be observed after the first seven stimuli. Spike activity is then blocked, being replaced by oscillating hyperpolarizing potentials. These continue despite cessation of stimulation, for 40 sec., before a 'spontaneous' spike reappears (2)–(3). (3) Full-sized spikes intermingled with incipient spikes and positive potentials

recorded both with ipsilateral and contralateral stimulation. In some instances the inhibitory effects are established after some stimuli, but without the remarkable oscillating behaviour already described.

When stimulation is discontinued, hyperpolarizing oscillations and inhibitory effects gradually subside, and after 20–100 sec., 'spontaneous' activity reappears, the membrane potential shifts towards negativity; positive potentials may appear intermingled with full-sized or incipient spikes, until the resting pattern of activity is finally re-established (Fig. 1). After some minutes of rest, renewal of stimulation is followed by earlier inhibitory effects, block being obtained with fewer stimuli, and eventually with a single stimulus. These blocking effects of long duration, especially when correlated with hyperpolarizing responses, suggest a mechanism different from fatigue—rather a mechanism of active inhibition. It is also improbable that fatigue could result from such a low frequency of stimulation, on occasions lower than the frequency of 'spontaneous' activity itself.

It is rather difficult to justify the use of the term 'habituation' to describe our observations, because of the conditions in which the experiments were carried out—with an isolated nervous system preparation, electrical stimulation of nerve trunks, and the short period of observation possible. Nevertheless, they confirm the existence of an inherent inhibitory mechanism in the nervous system of the snail, a mechanism which, put into action by repeated stimulation, could be the basis for a process analogous to habituation, at the neuronal level. Finally, as our observations seem to conform so neatly with Moruzzi's vivid suggestion regarding the mechanism of habituation, namely, that "monotonous repetition of an identical stimulus would bring about, by a phenomenon of temporal facilitation—an avalanching increase of activity in inhibitory neurons", we communicate these results under this rather provoking title, and as a schematic model for describing the phenomenon of habituation and discussing its hypothetical mechanism.

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Effects of Intensity of Driving Stimulus on the Shape of Membrane Action Potential of the Heart

An investigation of the influence of driving stimuli on the membrane action potentials of toad cardiac muscle fibres has been made. Endocardial surfaces of excised hearts were exposed and the transmembrane potentials of atrial and ventricular fibres recorded by means of glass-pipette microelectrodes.

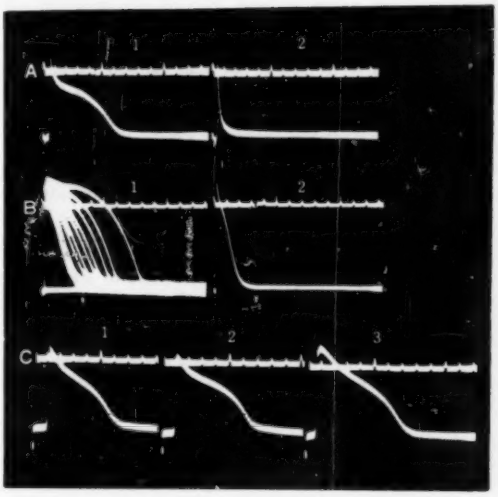

Fig. 1. *A*-1, Duration of action potential of an atrial fibre when using a threshold driving stimulus (7 V.), and *A*-2, the change in duration when driving stimuli were of twice threshold strength. *B*-1, The progressive shortening of the action potential when driving of quiescent atrial fibres was begun—the first ten beats. *B*-2 shows the steady state attained. *C*, Control atrial fibre action potential (1), after atropinization (terminal concentration of 1 in a million) (2), and when twice threshold driving stimuli were used on the atropinized tissue (3). Time is indicated in 100 (small pips) and 500 (large pips) msec. intervals. Calibration of voltage on the left base indicates −100 mV. from the extracellular potential (time-base)

As shown in Fig. 1*A*, duration of the action potentials of atrial fibres was reduced from 500 msec. to 59 msec. or by 88 per cent, when the intensity of the driving stimulus was made twice the threshold strength (Fig. 1 *A*–2). This effect was reversible and could be reproduced at will. Thus, by properly adjusting the intensity of driving stimuli the duration of induced action potentials could be controlled.

It was occasionally observed that similar changes in duration occur without the use of supraliminal stimuli. When atrial fibres, which had been quiescent for some time (about 2 min.), were driven with threshold stimuli, the action potential shortened progressively (Fig. 1 *B*–1) and attained a steady state of duration at about 22 per cent of the initial duration (Fig. 1 *B*–2) that of the first driven response.

Shortening of the duration of the action potential brought about by the procedure mentioned above was quite similar to the effect of acetylcholine or vagal stimulation. All three effects were antagonized by atropine. These findings suggest that a substance like acetylcholine is liberated by the driving stimulus and that the amount of the substance discharged is increased with an increase in the intensity of the stimulus.

In both atrial and ventricular fibres, the degree of reduction brought about by an increase in the intensity of driving stimuli was almost the same as that caused by maximal vagal stimulation. This result and the fact that the reduction was not uniform around the driving cathode suggest the possibility that liberation of acetylcholine occurs from intramural nerve endings or ganglia stimulated directly by the electrical drive itself.

The next problem is whether or not autonomimetic substances other than acetylcholine are also liberated by driving stimuli. The duration of the action potential elicited by threshold driving stimuli was

prolonged to some extent by administration of atropine (Fig. 1 *C*–2). After atropinization, increase in the intensity of driving stimuli still brought about certain changes in shape of the action potential, namely, a prolongation of its duration, rather than a shortening, an increase in amplitude of the overshoot, a slowing of the terminal phase of depolarization and initial phase of repolarization (Fig. 1 *C*–3). Since similar effects were obtained both in atrial and ventricular fibres by administration of epinephrine or norepinephrine as well as by sympathetic nerve stimulation, it is conceivable that increase in the intensity of the driving stimuli results in liberation of a sympathomimetic substance. This liberation might result from stimulation of intramural nerve fibres by driving stimuli as in the case of liberation of acetylcholine. In preparations not atropinized, these effects were not observed, probably because they were masked by those of the acetylcholine which was simultaneously liberated.

It is obvious that in electrically driven hearts the duration and shape of the membrane action potential can be widely varied, depending on the intensity of the driving stimuli. The possible liberation of the autonomimetic substances should always be taken into account in interpreting the results of experiments which involve electric stimulation of cardiac tissue.

Our thanks are due to Dr. Chandler McC. Brooks for reading the manuscript and making valuable suggestions.

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Interrelationship between Fat and Sugar Metabolism in Infant Rats

Rat milk contains a large amount of fat and protein[1]. The amount of sugar in this food is just sufficient to cover the energy needs of the infant rat for about 2 hr., and it is thus obvious that the energy required for the remaining 22 hr. of the day must come either from fat or protein. This is underlined by the fact that liver and muscle glycogen content, although falling transiently shortly after birth, soon return to higher levels[2].

In order to gain further insight into the ways in which individual nutrients are utilized by the infant rat the following experiments were performed: Rats aged 5 (suckling period) and 30 days (end of weaning), and adult animals (body-weight 200 gm.) of both sexes were starved for 24 hr., the 5-day-old animals at 30° C., the older ones at room temperature. They were then given 1·1 ml. of olive oil/100 gm. body-weight via a stomach tube, and were killed at different intervals. Liver glycogen content[3] and blood glucose-levels[4] were determined. It is evident from Fig. 1 that administration of olive oil to animals aged 5 days resulted in a rapid increase in the level of liver glycogen, while no such rise was observed in animals aged 30 days, or in adult rats. Blood glucose-levels remained unchanged in all age-groups.

The administration of 1·1 ml. oleic acid/100 gm. body-weight to 5-day-old rats resulted in a much smaller, and variable, rise in liver glycogen content and the blood glucose-level was slightly raised.

Fig. 1. Liver glycogen content in rats starved for 24 hr. and then given 1·1 ml. olive oil/100 gm. body-weight via stomach tube. Full line, rats aged 5 days; interrupted line, rats aged 30 days (the same type of curve was obtained for adult animals and for 5-day-old rats not given oil). Vertical lines indicate standard errors; each point is the average of at least 8 rats

It thus appeared that the glycerol contained in olive oil was responsible for the large rise in liver glycogen content found in 5-day-old rats. Administration of 2 ml. of a 2·5 per cent glycerol solution per 100 gm. body-weight, or administration of a mixture of oleic acid and glycerol corresponding to 1·1 ml. olive oil/100 gm., however, did not cause a rise in liver glycogen content, although hyperglycæmia was regularly found.

These results may be explained in several ways. Either fat gives rise to carbohydrate or fat spares sugars to a greater extent in the younger age-group. The first possibility can be rejected on theoretical grounds[5]; the second, however, may also be objected to since, following olive oil administration, glycogen accumulates in the liver and must be synthesized from some substance other than protein or amino-acids following the finding that gluconeogenesis from casein hydrolysate is much lower in sucking rats than in older animals[6]. Finally, there remains the possibility that triglycerides are transported differently in infant rats, as is also indicated by other results[7], and are transferred across the intestinal wall as such and broken down elsewhere, the glycerol being used for synthesis of liver glycogen.

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Generalized Skeletal Response on Local Trauma in Young Rats studied by means of ^{45}Ca-Metabolism

In connexion with following-up deviations in metabolism of calcium in bones in young animals after local injury by Roentgen irradiation, we wished to be convinced about the effect of other kinds of physical traumatism on the metabolism of calcium in bones. For this purpose we chose electric current for several reasons: in the first place, almost nothing is known about deviation in metabolism of bones injured by electric current, and secondly, because the entire question of the effect of such trauma on bones has been relatively little studied. Electro-trauma is quite easily carried out. It is also known that the majority of wounds in electro-trauma quickly heal without suppuration so that when experimenting it is possible to exclude undesired suppuration as a complication which could misrepresent the observed results. In case of other surface injuries, for example, radiation damage, torpid ulcers arise which are the seats of infection, causing local irritation which may meet with a response in the entire organism.

In our experiments we used male rats of the Wistar strain about 10 weeks old, each weighing 120–130 gm. We wounded them in the upper part of the shank on the back right limb by discharging a condenser, the capacity of which was 80 μF., loaded at a potential of 2,000 V.

Thus only one discharge penetrated across the limb. The rats were then divided into groups of five, and 20 μc. of $^{45}CaCl_2$ in 1 ml. physiological salt solution were applied intraperitoneally after 4, 10, 17, 24 and 38 days after injury. The rats were killed 48 hr. after addition of the isotope, and the tibias of the injured limbs dissected. The control limbs of the injured animals and the tibias of a control group of animals treated with isotope but not subjected to electro-trauma were also removed. Besides the tibia, we also took out the shoulder blade of all animals. With all the bones we recorded the weight of the dry bone and the ash after burning, measured the entire contents of bone calcium, and determined the specific activity of the calcium-45.

Four days after the injury, differences appeared in the weight of the dry bone, ash and calcium content of the tibias of the injured animals in comparison with

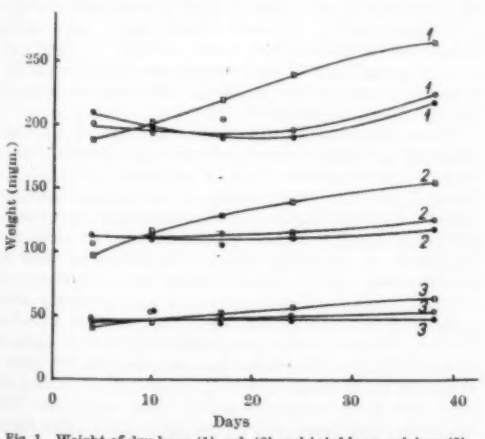
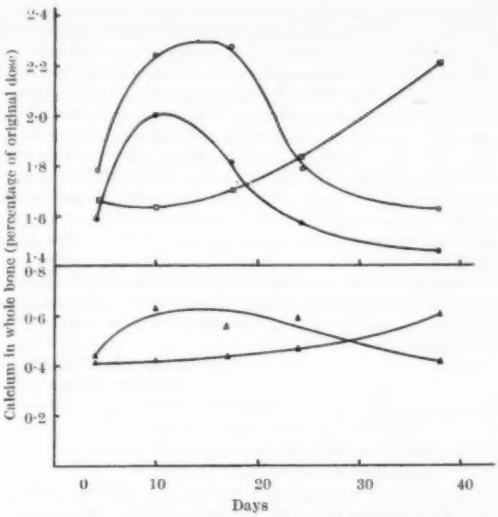


Fig. 1. Weight of dry bone (1), ash (2) and total bone calcium (3) of rat tibias. □, Control group; ○, traumatized tibia; ●, non-traumatized tibia



Figs. 2 and 3. 48-hr. accretion of calcium-45 in the tibia (above) and scapula (below). □, Tibia in control group; ○, traumatized tibia; ●, non-traumatized tibia; ▲, scapula of control group; △, scapula in traumatized animals

the control group (Fig. 1). All values showed a tendency to fall, followed by a much slower incline and restitution than in the uninjured animals. At the same time certain differences in weight appeared even in uninjured limbs of wounded animals, showing that a general reaction results from a local trauma. These changes occurred not only on the bones of the limbs but were also evident on the scapula, which is a bone of differently growing type from that of the limb, and is situated far from the injured place.

Distinct and important changes are evident when tracing the specific activity by measuring the values of calcium-45 in injured and uninjured bones. Fig. 2 shows the 2-day accretion of calcium-45 in the tibia and Fig. 3 in the scapula. It shows that in the bones of injured animals an increased accretion of isotope at first took place in all bones, again indicating the general response of calcium metabolism in the skeleton. When comparing Fig. 1 and the weights, it is surprising to find that while the weight of dry bone, ash and total bone-calcium content show a decline, the specific activity increases.

Calcium metabolism depends on a number of factors[1–4] the most important of which are accretion, resorption and calcium exchange. In comparing the results of our experiments, which follow accretion for 2 days, changes are evident in accretion values of calcium-45 in injured and uninjured bones of the experimental animal, changes which are expressions of local and general reactions as a result of local traumas. In comparing the results with the values of weight, it is shown that, after injury, not only the accretion is increased, but also the resorption of calcium (even more than accretion), so that the injury causes deep interference in the metabolism of calcium in the entire skeleton.

One other interesting inference, which follows from measuring and observing these values, is that in young animals even at the end of the experiment (about 40 days after injury) the conditions of metabolism had not become normalized. Although the skin wounds after electro-trauma were healed without

complications within ten days of the injury—healed in such a way that no traces of the transit of current were seen macroscopically—the disturbance of calcium metabolism and the response to local trauma remains as is shown by the dry-weight, ash, and calcium content of measured bones. Hence, the metabolic changes which result from local injuries to growing organism can persist for some time after healing. A similar reaction was noticed not only after electro-trauma injury, but also as a result of radiation injury[3], showing that this general response is the natural reaction of growing organisms to local trauma.

Details of the conditions of accretion and resorption of radiocalcium after local electro-trauma has been published in *Archiv für orthopädische und Unfall-Chirurgie*[5].

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Number of Recirculations of Chick Embryo Erythrocytes

It has recently been shown by Allison[1] on the grounds of cardiac output × erythrocyte life-span/blood volume that in spite of quite different erythrocyte life-spans in man, dog and rat the average number of times an erythrocyte is oxygenated and deoxygenated, that is, the number of recirculations, is in all three species of the same order, about 180,000 times. It might be of interest to determine if this relation is valid for embryonic erythrocytes also, and for their various lines respectively. Unfortunately, only incomplete data or none at all are available for mammalian embryos, though values covering nearly the whole incubation period have been published for chick embryos.

Using Allison's formula it was found that the number of recirculations of nucleated adult hen's erythrocyte is between 147,150 and 186,300, that is, in the range valid for non-nucleated erythrocytes of adult mammals[2].

Allison's formula in its original form is generally not suitable for calculation of embryonic erythrocyte recirculations because the cardiac output and the increase in blood volume and the absolute number of erythrocytes of one generation changes as development proceeds. For this reason we suggest the following procedure: for each day of incubation the number of recirculations is multiplied by the corresponding absolute number of erythrocytes of one line present in circulation (taken from their survival curve). The sum of these products over the whole incubation period will be divided by the maximal number reached by the erythrocyte line during incubation. Thus the average number of recirculations one erythrocyte undergoes will be obtained.

For each day of incubation starting with the second, the number of recirculations was calculated from Hughes's[3] data for stroke volume (data published by Hughes are for both ventricles together, and must therefore be gradually reduced starting with the fourth day to one-half from the seventh day onwards because of the development of allantoic circulation) multiplied by heart-rate value[4]. The product yielded the cardiac output/min. Thereafter the cardiac output values were multiplied by 1,440 min. (24 hr.) and divided by the corresponding blood volume[5]. So the average number of recirculations of the entire circulating blood/day of development was estimated. The average number of recirculations in a day's interval increase from 362 between the second and third day of incubation to 6,145 between hatching (20th day) and the first post-embryonic day (Fig. 1*a*). Because the results on the stroke volume[3] cover the period from day 2·5 to day 17 only, the border values on both sides have had to be extrapolated (dotted line in Fig. 1*a*). The error of this extrapolation is, however, of little bearing because the corresponding values in both survival curves (Fig. 1*b*, *c*) are low.

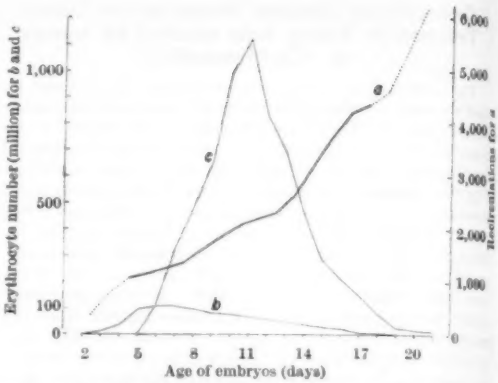

Fig. 1. (*a*) Number of recirculations from the second day of incubation until the first postembryonic day; survival curves of primitive (*b*) and definitive erythrocytes with round nuclei (*c*) during the same period

Both survival curves (absolute number of erythrocyte lines concerned present in circulation) are approximately of triangular shape and are practically limited to the embryonic period. That of the primitive erythrocytes[6], the first generation of erythrocytes (*E* I) starts on the second day of incubation with a maximum on the seventh day, while that of the definitive erythrocytes with round nuclei[7], the second generation of embryonic erythrocytes ($E\ II_1$), which appears as late as on the fifth day, reaches its maximum on the eleventh day.

From these results the average number of recirculations for a primitive erythrocyte was calculated to be 14,452 and quite a similar number (13,935) was found for a definitive erythrocyte with round nucleus. These values are most probably maximal, because the data for stroke volume probably err, according to Hughes[3], on the high side. That means that the average number of recirculations of two generations of chick embryo erythrocytes is considerably lower than in hens, being less than 10 per cent of adult values. This is not proportioned to the ratio of average erythrocyte life-spans concerned—30 days in hens[8] as compared with 8·5 days[9] for *E* I and 5·7 days[7] for $E\ II_1$ respectively in chick embryos. This indicates that there will be perhaps some other factor or factors besides that of the metabolic wear connected with ionic fluxes across the erythrocyte mem-

brane, as suggested by Allison, which play their part in the extremely short life-spans of chick embryo erythrocytes. One of these factors might be the high degree of immaturity at which the chick embryo erythrocytes are poured out into the blood stream[9].

A full account of our calculations is to be published elsewhere[2].

Future investigations will show if this relatively small number of recirculations holds good also for mammalian primitive erythrocytes. There are indications that their average life-spans are also about one-quarter of that found in adult mammals[10].

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PHARMACOLOGY

Stimulation of Uptake of Calcium-45 in the Adrenal Gland by Acetylcholine

Recently, Douglas and Rubin[1] have suggested that acetylcholine, the physiological transmitter of sympathetic nerve effects at the adrenal medulla, evokes catecholamine secretion by causing calcium ions to penetrate the medullary cells. Our experiments with calcium-45 have now provided further evidence consonant with this idea.

Adrenal glands from nine cats were perfused *in vitro* with Locke's solution. One gland from each animal was used to determine 'resting' uptake of calcium and the contralateral gland stimulated with acetylcholine. Both glands were perfused with Locke's solution containing calcium-45 for about 10 min. during which time one was given acetylcholine in a concentration (10^{-5} gm./ml.) sufficient to cause a brisk secretion of catecholamines. Thereafter, they were perfused with Locke's solution containing only calcium-40 and measurements were made of the efflux of calcium-45. Loss of calcium-45 from the perfused glands was at first very rapid, but it slowed after about 50 min. and the decline in activity in the glands thenceforth followed a simple exponential course. It was assumed, on the basis of the work of others on muscle[2,3], that by this time the extracellular calcium-45 had been completely washed out. One hundred minutes after beginning the washout, stimulated and unstimulated glands were separated into medulla and cortex and their radioactivity determined.

The glands exposed to acetylcholine contained more radioactivity than the unstimulated glands. On a weight basis, the medulla was several times more active than the cortex. Comparison of the stimulated and 'resting' medullæ indicated that during perfusion with acetylcholine the rate of calcium uptake was increased about eight-fold. A number of similar experiments were carried out with potassium, which is also known to evoke adrenal secretion. Potassium (56 m*M*) also caused an increased uptake of calcium-45, with the medulla again showing the greatest rate of uptake. This stimulant effect of potassium on calcium influx persisted in the presence of hexamethonium sufficient to suppress indirect effects due to stimulation of nerve endings present in the gland, and was presumably due to depolarization of the medullary cells.

We observed incidentally that acetylcholine and potassium also increased the rate of uptake of calcium-45 by the cortex, although to a lesser extent. This effect was too great to be accounted for by incomplete separation of medulla from cortex. It may be related to a stimulant effect of acetylcholine on adrenocortical secretion, such as Rosenfeld[4] observed in perfused calf adrenals.

The finding of increased uptake of calcium during exposure to acetylcholine or potassium is consistent with the idea that acetylcholine evokes catecholamine secretion by causing calcium ions to penetrate the adrenal medullary cells and that this penetration may be brought about by depolarization[1]. The finding also extends the remarkable parallelism previously noted[1] between the two sets of evidence implicating calcium in 'stimulus-secretion coupling' at the adrenal gland and in 'excitation-contraction coupling' in muscle.

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Pharmacodynamical Effects of Asarone and β-Asarone

Dandiya *et al.*[1,2] have determined the effect on the central nervous system of *Acorus calamus*, a drug used in the Indian system of medicine for various ailments including some of the mental disorders. In the present work two fractions 'asarone' and 'β-asarone' (isolated by Baxter and Kandel) of the volatile oil of *Acorus calamus* have been investigated with regard to effects on the central nervous system and other pharmacodynamical actions which these drugs have.

The prolongation of hypnotic activity of (i) pentobarbitone, (ii) hexobarbitone, and (iii) ethanol was investigated in white mice. Asarone and β-asarone were given in different groups of animals intraperitoneally in doses of 50 mgm./kgm., followed 15 min. later by one of the anæsthetic agents mentioned. The sleeping time was recorded in the manner described in refs. 1 and 2. It was observed that both asarone and β-asarone significantly ($P < 0.01$) prolonged the sleeping time of all the anæsthetic agents mentioned, for example, the mean sleeping time due to pentobarbitone alone, of 101·6 ± 14·5 min., was raised to 254·2 ± 18·8 min. when the animals were pretreated with β-asarone and to 206·4 ± 28·3 min. when the animals were pretreated with asarone.

It was also observed that the hypnotic potentiating property of β-asarone was significantly more ($P < 0.05$) than that of asarone in these doses against all these anæsthetic agents. Asarone or

β-asarone in these doses exerted no effect on the spontaneous motor activity of the animals in contrast to the increased motor activity observed with all the anæsthetic agents mentioned. However, the spontaneous activity of untreated animals was definitely reduced by asarone or β-asarone.

Both these agents caused a significant fall in rectal temperature of mice ($P < 0.01$). The fall was maximum in the first 30–45 min. and lasted 2–3 hr. and the recovery to the normal was attained in about 5 hr.

Anticonvulsant action of asarone and β-asarone was studied in ninety albino rats. Convulsions were induced by electro-shocks, or 'Metrazol' or 'Picrotoxin'. It was seen that β-asarone in an intraperitoneal dosage of 20 mgm./kgm. failed to influence the electro-shock seizures. Asarone in a dose of 20 mgm./kgm. intraperitoneally caused reduction in the incidence, duration and severity of extensor tonic phase induced by electric shocks. Asarone in a dose of 50 mgm./kgm. gave protective action against shocks induced by 'Metrazol' when prevention of extensor tonic spasm and death were considered as the protective end-points. The occurrence of both these endpoints was markedly reduced in animals treated with asarone. β-asarone, on the other hand, potentiated the lethal action of 'Metrazol'. However, both the compounds potentiated convulsions induced by 'Picrotoxin'. β-asarone itself in 50 mgm./kgm. doses intraperitoneally caused mild generalized myoclonic convulsions in rats; this property was lacking in asarone.

Effect on the spontaneous behaviour pattern was studied in eight cats according to the method in ref. 3. Both these compounds reduced the sociability score. Similar results were obtained with other tranquillizers like reserpine and chlorpromazine. The influence on conditioned escape and avoidance responses on 44 rats was investigated. The rats were trained to develop these two reflexes by the method in ref. 4 (with slight modifications). It was seen that the escape phenomenon (the rat jumping out of the cage even before the presentation of the conditioned stimulus, namely, bell) was abolished in 25 per cent of the trials and conditioned avoidance behaviour was abolished in 10 per cent of the trials, after both asarone and β-asarone. This percentage loss in these two reflexes was significant as compared with control data.

Frog heart perfusion experiments revealed that both asarone and β-asarone cause stoppage of heart in diastole in quite low concentration. However, β-asarone appeared to be more potent than asarone.

Isolated pieces of rabbit intestine were fixed for investigating the influence of these compounds on the longitudinal movements and the tone of the intestine. It was seen that both asarone and β-asarone reduced the tone and caused diminution in the longitudinal movements. β-asarone was found to be much more potent than asarone. Rhythmicity of the isolated uterine strip was reduced by both these agents.

Anti-acetylcholine actions for both these agents were investigated on the following preparations: (1) isolated guinea pig ileum; (2) isolated uterine strip of rat; (3) dog's tracheal muscle preparation; and (4) frog rectus. Both asarone and β-asarone were found to have anti-acetylcholine actions on these preparations and here, too, β-asarone was more potent than asarone.

So both asarone and β-asarone possess many pharmacodynamical actions quite similar to some of the well-established tranquillizers. β-asarone appears to be more potent than asarone and the influence of these compounds on electro-shocks and 'Metrazol' shocks differs. β-asarone itself causes generalized convulsions and potentiates the 'Metrazol' seizures, while asarone has a definite tendency to protect against 'Metrazol' convulsions and modify electro-shocks.

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HÆMATOLOGY

Haptoglobin and Transferrin Types in Peruvian Indians

Recent reports on the incidence of the serum haptoglobin types of American Indians have included observations on natives of Alaska[1], south-western United States[2,3], southern Mexico and Guatemala[4], Venezuela[5], and Chile[3]. The incidence of the Hp^1 gene, shown in Table 1, is usually higher than that found in the population of western Europe[4] (gene frequency 0·32–0·43, mean about 0·39). In several tribes, the occurrence of Hp^1 is as frequent as that reported in the various Bantus of Africa[4] (0·49–0·87). This finding is of particular interest when compared with the low incidence of Hp^1 (0·09–0·28) in Asiatic populations[2,4]. Since genetic drift is often responsible for marked fluctuations in the concentration of given genes in comparatively isolated areas, more observations are necessary to confirm these apparent differences. We have investigated the haptoglobin (and transferrin) types of two Peruvian Indian groups.

Plasma specimens were obtained from 56 Aymara-speaking Indians of Jaillihuaya, who have little, if any, European or African admixture, and an additional

Table 1. Distribution of Haptoglobin Types in North, Central and South American Indians

Population	No.	Haptoglobin phenotype (per cent) 1–1	2–1	2–2	0*	Hp^1 gene frequency
Alaska (ref. 1)						
North Athabascan	202	17·3	48·5	31·2	3·0	0·42
Tlingit	82	19·5	46·3	31·7	2·5	0·44
South-west U.S.A.						
Apache (ref. 2)	98	34·6	48·0	17·4	0	0·59
Navajo (ref. 3)	267	21·3	46·1	32·6	0	0·44
Central America (ref. 4)						
Non-Mayan	189	32·8	49·2†	17·9	0	0·57
Mayan	418	33·4	50·2†	15·8	0·6	0·59
Lacandon	31	77·4	12·9	0	9·7	0·90
South America						
Venezuela (ref. 5)						
Hybrids	208	27·4	54·8	17·8	0	0·55
Irapa	129	0·8	39·5	59·7	0	0·21
Paraujano	114	28·6	49·6	21·8	0	0·53
Macolta	74	16·2	54·1	29·7	0	0·43
Maquiritare	59	45·8	30·5	23·7	0	0·61
Chile (ref. 3)						
Araucanian	34	58·8	32·4	8·8	0	0·75
Peru						
Aymara	56	50·0	42·9	7·1	0	0·71
Quechua	117	54·7	38·5	6·8	0	0·74

* No visible haptoglobin, or unclassified.
† Includes two examples of *Hp* 2–1 (mod).

117 specimens from the Quechua-speaking Indians of Paucarcolla. From work on their blood groups, these subjects were calculated to have a White admixture of about 1·1 per cent and a Negro admixture of about 14·6 per cent[7,8], although no aberrant hæmoglobins or deficiencies in glucose-6-phosphate dehydrogenase were encountered[9]. The details of collection and distribution of samples have already been described[9].

Starch-gel electrophoresis was performed by Smithies' method[10], using Poulik's discontinuous buffer system[11] and a staining procedure outlined elsewhere[12].

No difficulties in interpreting the haptoglobin patterns were encountered, since all specimens contained adequate quantities of the hæmoglobin-binding protein.

There were no unusual phenotypes, such as the *Hp* 2-1 (mod) type which is a characteristic of 10 per cent of American Negroes[13].

Transferrin phenotype *C* was found in all the subjects except one, whose phenotype was B_2C. Transferrin CD_1, which occurs in about 10 per cent of American Negroes[14], and the recently described $B_{e-1}C$ type[3], found in about 8 per cent of Navajo Indians, were not encountered.

The haptoglobin phenotype distribution in the two Peruvian groups is compared in Table 1 with data on other Indians of North, Central and South America. The marked elevation in Hp^1 gene frequency cannot be considered to be due to Negro admixture in the Aymara-speaking Indians, and Negro admixture could only account for a moderate degree of elevation in the Quechua.

It has been suggested[4] that an increasing frequency of the Hp^1 gene in native populations occurs in the following order: Asia, Alaska, North America, Central and South America. That this apparent cline might reflect some regional selective advantage(s) is an attractive hypothesis. Further work on these and other populations may eventually lead to the elucidation of mechanisms responsible for the maintenance of haptoglobin polymorphism throughout the world.

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Serological Evidence of a Chromatographic Sub-fractionation of Human 7*S* γ-Globulin

PREPARATIONS consisting of the electrophoretically slowest migrating part of the 7*S* γ-globulin were prepared by means of preparative zone electrophoresis. Individual preparations were obtained from normal serum and from the serum of an *Rh*-immunized individual. Preparations from pooled plasma were obtained from commercially available Cohn fractionated γ-globulin (supplied by AB KABI, Stockholm). All preparations showed *Gm*(a+) character when tested in a serum-grouping system according to Grubb[1,2]. On immunoelectrophoresis with different rabbit antisera against human whole serum (supplied by Behringwerke, W. Germany) the γ-globulin preparations showed the character of 7*S* γ-globulin. No β_{2A} or β_{2M} was present.

These 7*S* γ-globulin preparations were subjected to hydroxyl apatite chromatography according to Hjertén[3]. The protein preparations dissolved in 0·02 mole phosphate buffer, *p*H 7·9, were applied to columns equilibrated with the buffer. The protein was eluted with the same buffer by a stepwise increase of the molarity of 0·03–0·65. As a rule all the protein was eluted in the steps up to 0·09 *M*. After dialysis against buffered saline (*p*H 7·2) and adjustment of the sample by ultrafiltration to equal protein concentration (as determined by a modified Folin method and by the Kjeldahl method), the sub-fractions were analysed and compared in the following way.

Immunoelectrophoresis revealed a somewhat higher electrophoretic mobility of the fractions eluted by phosphate buffer of lower molarity than of fractions eluted at higher molarity. Furthermore, the former type of γ-globulin showed a double precipitin line consisting of two discrete parallel lines, while the latter type showed a sharp single precipitin line (cf. Heremans[4]). This difference was more or less pronounced depending on which antiserum was used.

As already pointed out the γ-globulin starting materials used in the experiments were known to inhibit agglutination in a *Gm* grouping test system. This activity was now tested in the sub-fractions obtained by the hydroxyl apatite chromatography. The agglutinating system used consisted of constant amounts of *O Rh*(+) human red cells sensitized by incomplete *Rh*-antibodies and a rheumatoid serum of anti-*Gm*(a) character. The γ-globulin sub-fractions, of equal protein concentration, were added in two-fold serial dilutions to the agglutinating system. In all cases a higher agglutination-inhibiting activity was

Table 1. SEROLOGICAL ACTIVITY, AT EQUAL PROTEIN CONCENTRATION, OF 7 *S* γ-GLOBULIN SUB-FRACTIONS FROM HYDROXYL APATITE COLUMNS ELUTED AT DIFFERENT MOLARITY OF PHOSPHATE BUFFER (*p*H 7·9) EXPRESSED AS (TITRE)$^{-1}$

Fraction eluted at molarity	*Gm*-agglutination inhibition *	Sensitizing activity towards *O Rh*(+) red cells revealed by : Anti-γ serum †	Rheumatoid arthritis serum †
0·04	4	—	—
0·05	16	—	—
0·06	32	1	—
0·07	128	2	1
0·08	64	4	2

* To an agglutinating system consisting of *O Rh*(+) red cells sensitized by incomplete anti-*Rh* antibodies and diluted rheumatoid arthritis serum of anti-*Gm*(a) character two-fold dilutions of the different *S* 7 γ-globulin sub-fractions were added.

† A constant amount of *O Rh*(+) cells was added to two-fold dilutions of the different 7 *S* γ-globulin sub-fractions. After incubation at 37° for 2 hr. and subsequent washing, the agglutinability of the cells was tested with a rabbit anti-human γ-globulin serum and with the anti-*Gm*(a) rheumatoid arthritis serum.

found in the sub-fractions eluted by buffers of higher molarity than in fractions eluted by buffer of lower molarity. In the different experiments, the largest difference in this respect between sub-fractions originating from the same γ-globulin preparation varied 2–5 titre steps.

The possibility that this difference could be explained by an enrichment in the more active sub-fractions of aggregated 7*S* γ-globulin, which may have a high agglutination-inhibiting activity in the *Gm* grouping test system[3], was excluded by the following experiment. γ-Globulin sub-fractions obtained by hydroxyl apatite chromatography were submitted to zone ultracentrifugation in a sucrose gradient. The top fractions in this way freed from any fast-sedimenting 7*S* γ-globulin aggregates were recovered and tested in the *Gm* grouping system. The same difference in agglutination inhibition was observed as before ultracentrifugation.

The serological investigation of the γ-globulin sub-fractions of the serum containing incomplete *Rh*-antibodies is shown in Table 1. Besides the differences mentioned above, an enrichment of the *Rh*-antibodies in the sub-fractions eluted by buffer of high molarity was observed.

These observations thus indicate that hydroxyl apatite chromatography of human 7*S* γ-globulin may give sub-fractions differing in serological character.

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PATHOLOGY

Intracellular Response to an Iso-immune Reaction at the Surface of Ascites Tumour Cells

The cytotoxic effect on mouse ascites tumour cells treated *in vitro* with various antibodies has been shown to require the presence of complement[1,2]. In the absence of complement the cells appear to be normal when viewed by phase contrast microscopy[3]; they retain their capacity to exclude trypan blue[3] and to metabolize glucose[4]. The only changes which have been reported are slight alterations in the fine structure of the cell surface, which were thought to favour agglutination by rabbit antibody directed against ascites cells[3].

There is strong evidence, from hæmagglutination work, that some iso-antigens of the *H*-2 system[4] are present on the surface of mouse erythrocytes[5]. The present investigation was undertaken to determine whether such iso-antigens could be demonstrated on the surface of *EL4* ascites cells, and whether histochemical methods could be used to reveal the effect on the cell of an iso-immune reaction at its surface, in the absence of complement.

Iso-antisera were prepared in *BALB/c* strain mice against *EL4* tumour cells resident in *C57BL* strain mice by immunization with tumour cells mixed with Freund's complete adjuvant. The mice and tumour were the generous gift of the late Dr. P. A. Gorer. The cytotoxic titres[2] of these antisera, in the presence of complement, varied from 1/64 to 1/256. In the absence of complement, iso-antibody caused negligible agglutination of cells even when present at as high a concentration as 1 vol. antiserum: 1 vol. cell suspension containing 2×10^7 cells/ml. This was in marked contrast to the strong agglutinating effect of rabbit antibody which was observable even with rabbit antiserum diluted 256 times.

It was first necessary to confirm that the mouse iso-antibody did react with surface antigens. This was effected by incubating suspensions of *EL4* cells with mouse antiserum (preheated for 30 min. at 56° C.) in the absence of added complement. That the antibody was located exclusively on the cell surface was observed by subsequent staining of air-dried smears of washed cells with a rabbit anti-mouse globulin which had been conjugated with fluorescein isothiocyanate.

It was remarkable that in these circumstances, which were expected to produce purely surface effects, marked cytoplasmic changes were observed when histochemical techniques were applied to air-dried smears. Thus, exposure of the cells to iso-antiserum alone, at 37° C. for 15 min., in the absence of complement, resulted in marked activation of lysosomal acid phosphatase[7]; there was also simultaneous unmasking of cytoplasmic phospholipid, particularly in discrete granules, as shown by the acid hæmatin technique[6]. The stimulation of glucose dehydrogenase activity observed under similar conditions could have been a non-specific effect since it was also observed after incubation of these cells with normal serum.

The immunofluorescent results indicated that this iso-antibody acted solely at the surface of the cells under these experimental conditions. If this were true, then the effect of the immune reaction at the cell surface in causing changes in intra-cytoplasmic particles was surprising.

In homograft rejection, circulating antibody may act synergically with immunologically competent host cells, though the extent to which complement is involved is uncertain. It is possible that intra-cytoplasmic effects of iso-antibody acting at the donor cell surface may play some part in the mechanism of rejection.

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A Carcinogenic Action of Testosterone, provoking Uterine Tumours in Mice

THE literature concerning the induction of tumours by hormones is very extensive[1-4]. Œstrogens especially appeared to play an important part in hormonal carcinogenesis[5]. Evidence of a carcinogenic action of androgens is very scant. Horning[6] observed 3 theca-cell ovarian tumours in rats and 2 adrenal cortical tumours in hamsters after long-term treatment with testosterone. Also, Kirkman[7] suggested that testosterone propionate may act as a non-specific carcinogen in the hamster.

In our experiments one pellet of 1–2 mgm. testosterone propionate was subcutaneously implanted into female mice of the *F*1 hybrid (*C57BL* × *dba*) twice a week. The treatment was started at the age of 1½–3 months and continued until the mice had to be killed because of their bad condition.

At post-mortem examination a surprisingly high percentage of uterine tumours was found (Table 1).

Table 1. UTERINE TUMOURS INDUCED BY TESTOSTERONE

	No. of mice*	No. of mice with tumours	No. of mice with lung met.	Average survival time (months)†
♀♀ F_1 (*BD*)	14	6	3	18·8
♀♀ F_1 (*BD*)	16	9	3	14·7
♀♀ F_1 (*BD*)	12	11	4	15·3

* Surviving the testosterone treatment for 10 months or more.
† No difference was found in the survival time of the tumour-bearing and the non-tumour-bearing mice.

In 26 of the 42 mice treated with testosterone uterine tumours were observed, and in 10 of the tumour-bearing mice metastases were present in the lungs.

Most of these tumours were found either in the uterine cervix or in the unpaired uterine part. Only a few tumours were located in the horns of the uterus. The size of these tumours varied considerably. The largest diameter was about 25 mm. and the smallest 4 mm. The tumours were always strictly limited to the uterus and the vagina and no other tissue of the peritoneal cavity was involved. The surfaces of the cut tumours showed mostly a pink colour, but sometimes necrotic or hæmorrhagic areas were seen.

The histological pattern of the testosterone-induced uterine tumours was very characteristic and similar for the several tumours we have observed. In most of these tumours large trabeculæ of cells were found next to more solid parts. The trabeculæ formed locally branched papillæ inside large sinuses. Most of the tumour cells had a diameter varying from 20 to 30μ and contained an abundant fine granular cytoplasm which stained mostly basophilic. The nuclei were large and relatively clear with prominent nucleolus (Fig. 1).

Most of the tumours showed an infiltrative growth in the muscular layers of the uterine wall. This fact together with the appearance of lung metastases are distinguishing marks of the malignancy of these tumours.

In most of the mice bearing a uterine tumour as well as in those without a gross uterine tumour one or more small pink nodules were observed in the uterus. Macroscopically and microscopically these nodules showed close similarities to the gross uterine tumours. We think we are justified in considering these nodules as stages preceding the malignant uterine tumours.

These nodules developed in the stroma of the endometrium. The epithelium and the muscular layers were not involved. The origin and the histological aspects of the nodules are similar to the histological changes in the stroma of the endometrium during the first stages of pregnancy. On these similarities we base our hypothesis that the uterine tumours induced by testosterone are related to the decidua cells. The histological characteristics of these specific uterine tumours differ from the uterine carcinomas and uterine sarcomas so far described.

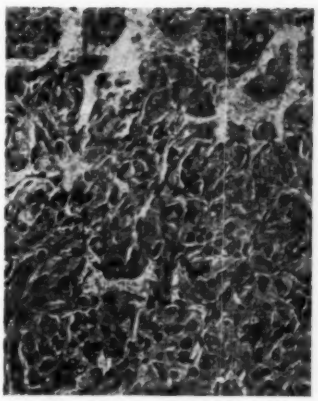

Fig. 1. Histological picture of a uterine tumour. (× 200)

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Deiodination of Thyroxine-^{131}I in Tumour-bearing Rats

IT has been shown that hyperthyroidism induced by the administration of large doses of triiodothyronine increased the radiosensitivity of tumours in rats and in human beings[1,2]. Later it was found that hyperthyroidism induced in this way significantly enhances the growth of a solid non-metastatic myeloid leukæmia tumour of the Sprague–Dawley rat, a rat fibrosarcoma of a local strain and the Ehrlich mouse ascites tumour[3].

In view of the profound effect of severe hyperthyroidism on tumour growth and its response to radiation, it became of interest to investigate the turnover of thyroxine in animals bearing these tumours.

The rate of deiodination of thyroxine was investigated by administration of a tracer quantity of labelled thyroxine and the amount of the inorganic iodide formed was determined by radioactive assay. To ensure complete retention of the iodide formed in the circulation, rats were surgically thyroidectomized 48 hr. before the turnover experiment. Tracer thyroxine, labelled with iodine-131 in the 3′ and 5′

positions, was injected into the vena cava following a bilateral nephrectomy. Blood samples were collected into heparinized test-tubes at 45-min. intervals for 5–8 hr. The serum was then separated and the iodine bound to protein was determined[4]. From the total values of serum iodine and protein-bound iodine the serum iodide concentration (per cent of injected dose per gm. serum) was calculated. The increase in iodide concentration with time was taken as an index of the rate of deiodination of thyroxine.

In the experiments performed on 150 rats it was found that the rate of deiodination (per cent thyroxine deiodinated per unit time) was higher in the animals bearing tumours than in the respective controls. Since age was one of the major factors affecting the rate of deiodination, all rats selected were of identical age. The differences between the average rates were 50 ± 10 per cent in the leukæmia tumour and 45 ± 10 per cent in the rats bearing fibrosarcoma, with a statistical significance of more than 99 per cent. In hypothyroid animals the difference in the rate of deiodination was even greater, amounting to 80 ± 15 per cent in the animals bearing fibrosarcoma as compared with their hypothyroid non-tumorous controls. In a similar manner old age was found to be another condition in which the difference between tumorous and control animals manifests itself emphatically; a difference of more than 150 per cent in the rates of deiodination was observed here. On the other hand, no significant difference in the rate of deiodination was found between animals with or without tumours in which hyperthyroidism had been induced artificially.

After the deiodination experiments the animals were killed and the specific activity of the tumours (per cent of injected dose per gm. tissue) was compared with that of the gastrocnemius muscle. The specific activity of the tumours was 3–5 times higher than that found in muscle and was comparable with that in the ovaries. A similar finding has been reported in the mouse mammary tumour using triiodothyronine[5].

The weights of the tumours ranged from 5 to 40 gm., constituting 2–25 per cent of the total weight of the rats bearing tumours. However, when the increase in rate of deiodination was related to the weight of tumour in each animal, or to the per cent body-weight constituted by the tumour, no correlation could be established.

Physiological variations between normal and tumour-bearing animals as described here are rare and are worth careful consideration. An increased rate of deiodination is generally associated with the hyperthyroid state, yet no indication of such a state is apparent in animals bearing tumours. As little is known about the mechanism of deiodination of thyroxine at the cellular level, it is premature to put forward an explanation for the enhanced deiodination.

The lack of correlation between the degree of enhanced deiodination and the mass of the tumour strongly suggest that the effect is due either to a change in the hepatic metabolization of thyroxine or to a certain factor of a systemic nature mediated by the presence of the tumour. The tumour thus does not appear to be the site at which the excess deiodination takes place. Should this effect prove to be associated with the presence of malignant tumours in general and should it occur also in human subjects afflicted with cancer, then the demonstration of an increase in the rate of deiodination of thyroxine may be of value for the early diagnosis of malignant growths which are not otherwise detectable.

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HISTOLOGY

Role of the Thymus in Polysaccharide Metabolism

It has been shown by a series of experiments[1–3] that the thymus plays an active and significant part in polysaccharide metabolism. It was demonstrated[1,3,4] that, unlike other lymphatic organs, stress and processes of tissue proliferation induced the emigration of cells from, and a mast-cell reaction in, the thymus. This reaction was preceded by the appearance of periodic acid–Schiff-positive cysts and of thymocytes containing periodic acid–Schiff-positive matter. It was possible to confirm these findings by demonstrating in tissue cultures[2] that the cells of the thymus showed a marked affinity for heparin[4] and decomposed heparin[2], which was much stronger than that of other cells (liver, spleen, heart, kidney) and even more pronounced than the heparin affinity of the lymph node, which ranks, in this respect, next to the thymus. Although these experiments revealed the prominent role of this organ in the metabolism of mucopolysaccharides, it seemed necessary to measure this activity by means of a more exact method.

It was with an indirect method and the use of isotopes that we investigated the correlation between thymus and acid mucopolysaccharides in the present experiments. Instead of labelled heparin we used labelled thionine (a dye): it combines with heparin *in vivo* so that radioactivity indicates the extent to which thionine is taken up by the organs and thus can be used as an indicator of their heparin metabolism. Thionine was labelled with sulphur-35 in our experiments for which 10 rats of 150 gm. body-weight were used. Each animal received intraperitoneally 4 mgm. of the dye. The animals were killed by a blow on the head 24 hr. after the injection; thymus, lymph node, spleen, liver and heart were removed, weighed and homogenized; radioactivity was then measured with an end-window Geiger–Müller tube and a scaler of type *EMG* 1872. Radioactivity in the blood was ascertained also. Results are shown in Table 1; values are given as percentages of total radioactivity introduced and refer to 100 mgm. of wet tissue.

Table 1

Organ	Radioactivity (percentage of total)	Standard deviation	Result of Student's t test
Thymus	2·52	0·18	Highly significant, $P < 0{\cdot}1$ per cent
Lymph node	0·152	0·012	Highly significant, $P < 0{\cdot}1$ per cent
Spleen	0·11	0·011	
Liver	0·12	0·003	
Heart	0·12	0·003	
Blood	0·007		

It can be seen that all tissues investigated, with the exception of the thymus and lymph node, took up approximately the same small quantity of dye. This seems to indicate active uptake or the combination of the dye with the existing acid mucopolysaccharides, since radioactivity in the blood was quite negligible. Though quantitatively low, activity was significantly higher in the lymph node, and outstandingly high in the thymus, about 20 times as high as in other tissues.

These figures are in good agreement with the results of earlier experiments: they show that the thymus plays a prominent part in the metabolism of acid mucopolysaccharides (of heparin in particular) and furthermore they show that although morphologically similar, the thymus on one hand, and the spleen and lymph node on the other, have different functions and are involved in different biological processes. It seems, moreover, that as regards polysaccharide metabolism, there is also a difference between lymph node and spleen; this, too, is in agreement with earlier observations according to which the lymph node is more or less capable, and the spleen incapable, of forming mast cells[2,5].

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Fixation of Muscle

I HAVE investigated recently the effect of various fixation methods on mammalian skeletal muscle. For this purpose the biceps brachii muscle of the albino mouse was chosen because of its convenient size and the fact that it can be easily dissected out. All the mice used were females weighing about 34·5 gm., the biceps muscles were weighed in each case, and all were found to weigh about 0·0155 gm.

The fixatives used were of the normal concentrations, 2 per cent osmium tetroxide being used in Champy's fluid and in Flemming's fixative. Following fixation, etc., the paraffin-embedded material was cut at 7·5μ and sections taken through the belly of this muscle were stained with Mallory triple stain. The outlines of the fibres were drawn on squared graph paper with the aid of a camera lucida. The average cross-sectional area and the standard error were determined in each case from a sample of 25 figures taken at random. In the case of fibre measurements of the living muscle, the fibres were teased out in Locke's mammalian Ringer solution, and their diameters were measured immediately. As the fibres were seen to be circular in transverse section, their cross-sectional area was obtained by treating them as cylinders. Direct cross-sectional area measurements were found to be impracticable because the living material tended to contract on cutting. The standard error of the living fibre sample was 106 sq. μ. The results are represented in the histogram (Fig. 1).

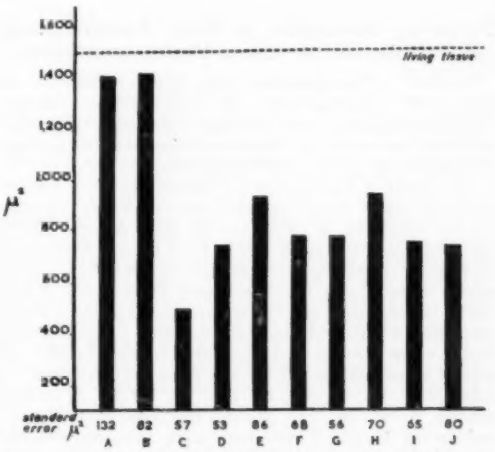

Fig. 1. Effect of various fixatives on fibre cross-sectional area (fixation time in parentheses)
A, Champy's fluid (42 hr.).
B, Flemming without acetic acid (42 hr.).
C, Formol calcium (12 hr.).
D, Bouin's (12 hr.).
E, Carnoy (3 hr.)
F, Dalton's (1 hr. and postchrome for 6 hr.).
G, Neutral formalin, neutralized with sodium hydroxide (48 hr.).
H, 2 per cent osmium tetroxide in acetone } freeze substitutions (1 week)
I, Carnoy
J, Methanol

The results of the freeze substitution technique[1] were surprisingly poor; these were repeated but the same extent of distortion occurred. Sections of kidney prepared at the same time and in the same way showed no distortion. In the case of muscle treated by the methanol freeze substitution technique, extensive breakage of the sarcolemma was noted. Champy's fluid and Flemming's without acetic acid are seen to cause little shrinkage, and the results obtained from these two osmium tetroxide fixatives are very close to those for the living tissue; the histological appearance of such sections is extremely good and the muscle spindles are very well preserved. It is often not practicable to use osmium tetroxide on a large scale, as it is relatively expensive and has only very low powers of penetration, thus limiting severely the size of the tissue which can be fixed. It would seem that a slight shrinkage is inevitable, as the fibres will lose their turgidity on fixation.

The other fixatives caused great distortion. This could be readily seen because of the polygonal shape of fibres in transverse sections as compared with the spherical or ovoid shape of those fixed in Flemming without acetic acid, Champy's fluid, and the living fibres. This distortion is probably due to a chemo-shortening of the fibrous connective tissue around the bundles.

In the light of these results, it seems most unfortunate that much of the work on the shape and size of muscle fibre has been carried out on material fixed in formalin.

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RADIOBIOLOGY

Detecting Reversion in *T4rII* Bacteriophage to r^+ induced by Ultra-Violet Irradiation

During investigations into the mechanism of ultra-violet mutagenesis in extracellular phage, the following test was developed for estimating the extent of reversion of bacteriophage *T4B* from *r*II to r^+ induced by ultra-violet irradiation.

All *T4r*II mutants were obtained in this laboratory by ultra-violet irradiation of *T4Br*$^+$ phage. 12 hr. cultures of *Escherichia coli B* and *K*–12 (λ), obtained in 1958 from E. Freese, were used in assays of *r*II and r^+ phage respectively. Agar media were those of Chase and Doerman[1]; broth media contained, per litre ion-free water, 10 gm. tryptone, 8 gm. sodium chloride, and 1 gm. glucose. Phage were diluted and irradiated in this broth. All assays were performed by the agar layer method of Adams[2]. To detect as few as 20–30 r^+ phage among 5×10^8 *r*II phage the concentration of bacterium *K*–12 (λ) per soft agar tube approached 2×10^9.

A 15-watt 'Sylvania' 17-in. low-pressure germicidal lamp was used to irradiate all samples at a distance of 67 cm. and at 4° C. Phage samples were distributed as two-drop aliquots on glazed white porcelain spot test plates which were agitated during exposure. Irradiated phage were handled in dim light to avoid photoreactivation. Under these conditions a standard inactivation curve, graphed as the logarithm of percentage survivors against ultra-violet dose, was linear to 0·001 per cent survivors; 55 sec. of ultra-violet irradiation resulted in a survival-level of e^{-1}.

Each of 12 *r*II mutant stocks was assayed on *B* and on *K*–12 (λ) to determine accurately the titre of total and of r^+ phage. Triplicate samples of each phage stock were irradiated to various survival-levels as indicated in Table 1. Two to three aliquots of these samples were then assayed on bacterium *K*–12 (λ) to obtain the titre of r^+ phage (background plus ultra-violet-induced mutants). Remaining aliquots of these samples were assayed on bacterium *B* to provide the exact survival-level.

Results are presented in Table 1. Clearly 5 of the 12 mutants revert to r^+ when irradiated with ultra-violet. The extent of reversion ranges from 1·81 $r^+/10^8$ survivors to $4{\cdot}2 \times 10^5$ $r^+/10^8$ survivors. Two other mutants (*UF*54 and *UF*147) may be weakly revertible but cannot be definitely classed as such since the proportion of r^+ phage per 10^8 surviving phage is so low as to make an accurate assay of their number unfeasible by this technique.

Control experiments by Krieg[3] ruled out the possibility that the observed increase in r^+ phage might be due to ultra-violet-induced selection for r^+ phage present in the stocks before irradiation.

This technique for detecting reversion differs from Krieg's[3] in the following points. (1) Ultra-violet-irradiated phage are directly assayed for their r^+ content with no intervening cycle of phage growth. (2) Our average number of lethal hits per phage was considerably lower than Krieg's[3], yet reversion was still demonstrable. (3) Our multiplicities of infection of bacterium *K*–12 (λ) with ultra-violet-irradiated phage during r^+ assay were of necessity less than 1. Krieg's[3] multiplicities of bacterium *B* during the first cycle of ultra-violet-irradiated phage growth were considerably greater than 1, and lead to multiplicity reactivation. The results presented here lead one to surmise that multiplicity reactivation is not a prerequisite occurrence for the ultra-violet-induced reversion of *r*II to r^+ phage.

The possibility is not ruled out that, when present, multiplicity reactivation may of itself lead to the production of revertants.

Different *r*II mutants appear by this simple test to differ appreciably in their ability to be induced to revert by ultra-violet-irradiation. Among the 5 *r*II mutants which could be induced to revert, the extent of reversion ranged from 1·81 to $4{\cdot}2 \times 10^5$ r^+ per 10^8 surviving phage. It is interesting that all those mutants which are most easily reverted by ultra-violet irradiation are also high-frequency spontaneous reverters. The compartmentalization of this small sample into ultra-violet-revertible and ultra-violet-non-revertible is suggestive of some specific mutagenic effect of ultra-violet light upon free phage. Investigations concerning this specific ultra-violet mutagenic effect on free phage, from r^+ to *r*II and from *r*II to r^+, will be published elsewhere.

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Table 1. Extent of Reversion of *T4r*II to r^+ induced by Ultra-violet Radiation

Mutant	n where $e^{-n} = S/S_0$	Stock titre $\times 10^9$	r^+_0	r^+_0 (S/S_0)	Total r^+ after ultra-violet irradiation	r^+ ultra-violet per 10^8 S	Reversion group
*UF*2	0·60	5·6		533	360	0	*NR*
			970				
*UF*2	9·9	5·6		0·003	0	0	
*UF*54	0·97	4·8		199	290	0·06	*NR*
			470				
*UF*54	6·3	4·8		0·8	0	0	
*UF*147	0·88	2·0		338	630	0·35	*NR*
			805				
*UF*147	5·3	2·0		4·03	1 plaque	—	
*UF*125	0·57	8·3		950	1,180	0	*NR*
			1,670				
*UF*125	7·4	8·3		1·01	2 plaques	—	
*UF*211*A*	1·6	15·0		1,230	1,010	0	*NR*
			6,150				
*UF*211*A*	7·7	15·0		1·35	0	0	
*UF*344*A*	3·4	10·0	10,700	353	950	1·81	R_w
*UF*165	1·9	10·0	3,300	495	480	0	*NR*
*UF*114	3·0	2·5	1,010	50·5	300	2·01	R_w
*UF*144	13·0	6·0	$1{\cdot}7 \times 10^7$	49·4	$6{\cdot}84 \times 10^5$	$4{\cdot}2 \times 10^5$	R_s
*UF*173	5·8	13·0	$1{\cdot}1 \times 10^5$	$3{\cdot}2 \times 10$	$3{\cdot}5 \times 10^3$	83	R_s
*UF*518*B*	8·0	14·0	$1{\cdot}1 \times 10^7$	$3{\cdot}8 \times 10$	$3{\cdot}7 \times 10^4$	$7{\cdot}44 \times 10$	R_s
*UF*50	0·39	2·1	0/10[9]	0	0	0	*NR*

n, Average number of ultra-violet 'hits' per phage where $e^{-n} = S/S_0$; S/S_0, percentage of survivors; r^+_0, titre of r^+ phage present per ml. phage stock before irradiation; r^+, ultra-violet, total r^+ after ultra-violet $- r^+ (S/S_0)$. Reversion group: *NR*, non-reverter; *R*, reverter; *s*, strong; *w*, weak.

* National Science Foundation Undergraduate Research Participation Programme.

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Effect of X-Irradiation on Self-Stimulation of the Brain

RECENTLY it has been shown that the brain is sensitive to low doses of ionizing radiation[1,2]. Prolonged exposure to X-irradiation decreases lever-pressing by rats[3]. Conditional aversion to saccharin results from exposure of rats to γ-radiation[4,5]. Because radiation affects psychological tests based upon food or fluid intake, we studied the effects of X-irradiation on rats trained to press a lever for electrical stimulation of the brain[6]. A single electrode was permanently implanted in the posterior hypothalamus of 8 *CFN* rats. After a training period of 6 months, the rats received 600 r. acute whole-body X-irradiation. Radiation characteristics were: 250 kVp.; 15 m.amp.; focus-object distance 70 cm.; filters, 0·21 mm. copper inherent, 0·5 mm. copper parabolic and 1·0 mm. aluminium; half-value layer 1·92 mm. copper; 22·9 r./min. measured in air.

Calibration of the machine was done with a Victoreen thimble r.-meter and output during irradiation was measured with a Radocon unit. On completion of the experiment, histological sections of the brain were compared with the de Groot atlas[7] to locate the electrode tip.

The responses of the animals can be divided into two groups. Those with high pre-irradiation rates (Fig. 1) had highly significant increases in the rate of lever-pressing on the day of irradiation. This was followed by return to, and a fluctuation within, the control values until the 17–19 post-irradiation day when there was a significant decrease in the rate of lever-pressing.

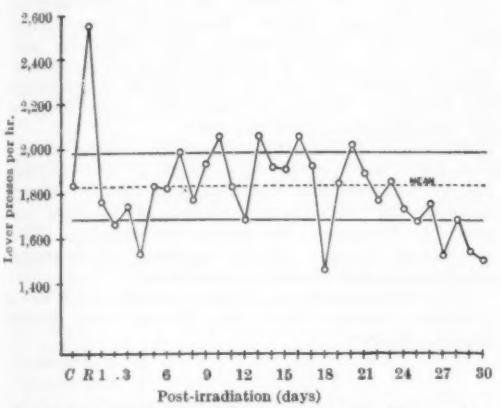

Fig. 1. Response of high-rate lever-pressing rat to 600 r. acute whole-body X-irradiation. The horizontal lines indicate the mean and standard deviation determined over a period of 6 months. The elevation of lever-pressing activity is highly significant ($P > 0{\cdot}001$). *C*, Control; *R*, irradiation day

The other group of 3 animals had low pre-irradiation rates (Fig. 2) and showed highly significant decreases in rate on the first post-irradiation day. These animals had difficulty in again attaining their pre-irradiation rates throughout the 30-day period of observation. Histological examination of the brains revealed that the rate of lever-pressing was not associated with any specific nucleus in the hypothalamus, because both high and low rates were obtained from nucleus arcuatus hypothalamic, nucleus dorsomedialis hypothalamic and area lateralis hypothalamic.

Although the usual transient loss in weight produced by the irradiation was seen, this effect apparently had

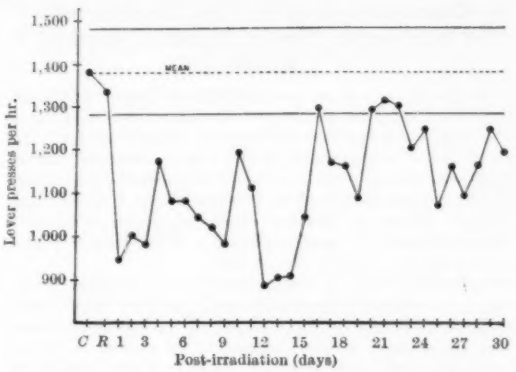

Fig. 2. Response of low-rate lever-pressing rat to 600 r. acute whole-body X-irradiation. The horizontal lines indicate the mean and standard deviation determined over a period of 6 months. The depression of lever-pressing activity is highly significant. ($P = 0{\cdot}01$). *C*, Control; *R*, irradiation day

nothing to do with the changes in performance of both groups of animals because they showed slight increases in weight during the 30-day observation period. These results indicate that self-stimulation of specific nuclei in the posterior hypothalamus may give high or low rates of response depending on the particular nucleus stimulated.

This confirms the observations of Hess[8] on the autonomic and somatomotor responses in the diencephalon, those of Gellhorn[9] on the autonomic areas and also those of Slusher and Hyde[10] on diencephalic control release of adrenocorticotrophic hormone. In all these cases, diametrically opposite actions were obtained by stimulation of similar areas. The depression of lever-pressing activity is much more prolonged than the stimulation of such activity. Thus, it would appear that the nuclei involved in these opposite actions may be directly affected by radiation, although the present experiments do not rule out the possibility that indirect and/or humoral agents from other areas in the body actually produced the effects observed. The question of direct versus indirect effects of the irradiation on the brain as well as the use of other electrode arrangements is now under investigation.

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Concentration of Inhaled Cerium-144 in Pulmonary Lymph Nodes of Human Beings

In the course of an investigation of fission products deposited in human lungs[1], we have also measured the radioactivity of pulmonary lymph nodes. In most cases investigated so far, the amounts of fission products found were too small to permit deductions about concentration of these substances in the lymph nodes. However, in some cases larger activities were observed and the occurrence of a concentration process could be clearly recognized.

Concentration of radioelements in lymph nodes may, in certain circumstances, produce high local radiation dosages. In evaluating radiation hazards due to inhaled radioelements it is therefore necessary to find out whether lymph nodes have to be considered as a 'critical organ'. Many factors must be taken into consideration in this connexion[2,3]; but the data required for this are only partly available so far. Data about the concentration of inhaled radioelements in lymph nodes of human beings have been reported only in one case, that of a man who had occupationally inhaled plutonium-containing aerosols for several years[5]. Further data on concentration in lymph nodes have been obtained in experiments with animals, chiefly with plutonium and polonium[2,3,5,6].

We wish to report three cases, in which our measurements give information about concentration of cerium-144 in human lymph nodes (Table 1). The lungs investigated were obtained from deceased persons, who had—like all people—inhaled the radioactive aerosol produced in nuclear test explosions in recent years. The major part of the cerium-144 detected in our measurements on lungs was probably produced in the high-yield test explosions carried out in 1957 and 1958. Cerium-144 is particularly suited for studying the behaviour of inhaled 'fall-out'-particles for the following reasons: (1) This fission product is present in fall-out largely in insoluble form[7]. (2) Because of its half-life (285 days) and fission yield, cerium-144 is present in larger activity than other fission products in the period of approximately 1–4 years after formation by nuclear fission (ref. 8).

The organs investigated came from older persons (58–81 years), who had lived in Vienna for at least several years and died here. After the routine autopsy pulmonary lymph nodes (Lymphonodi bronchopulmonales, bifurcationis, tracheobronchiales, paratracheales) were removed. This was facilitated by their dark coloration due to deposited anthracotic pigment, which is commonly present in city inhabitants. Lymph nodes and lungs were then ashed separately. In the ashes cerium-144 ($E\gamma$ = 134 keV.) was determined by gamma-spectrometry using a well-type NaI(Tl)-crystal. The spectrum was obtained in detail from 84 to 156 keV. by measuring 32 min. in each channel of 8-keV. width. In the cases reported here, the photo-peak at 134 keV. was clearly identified. We determined the area of the photo-peak above a 'background continuum', due in large part to the Compton continua of other radioelements and environmental radiation, and then calculated the amount of cerium-144 present by comparing with samples of known activity.

In the first group of samples listed in Table 1, the lymph nodes from three lungs were combined in order to increase the activity to be measured. Thus

Table 1. Cerium 144-Contents in Lungs and Lymph Nodes

Date of death	Sample*	Wet tissue mass, W (gm.)	Ash mass (gm.)	Date of measurement	Cerium-144 activity of whole sample, A ($\mu\mu$c.) and statistical error†	Ratio of specific activities (lymph node: lung) V‡
	BI/N	45	2·8	14/12/60	16·4 × (1 ± 0·34)	
29/11/60	BH/L	800	7·46	13/12/60	17·0	
30/11/60	BG/L	500	6·68	13/12/60	16·5	
29/11/60	BF/L	1,000	11·39	19/12/60	10·2	
	Sum	2,300			43·7 × (1 ± 0·30)	19
17/ 8/60	BQ/N	11	0·15	13/ 2/61	6·6 × (1 ± 0·69)	
17/ 8/60	BP/L	1,020	10·1	21/ 2/61	52·0 × (1 ± 0·23)	12
12/ 5/60	CG/N	5	0·25	11/ 2/61	5·6 × (1 ± 0·76)	
12/ 5/60	CF/L	1,150	11·8	24/ 2/61	20·0 × (1 ± 0·68)	64

* /N, lymph nodes; /L, lung.
† From calibration measurements for cerium-144: 1 c.p.m. = 5·1 $\mu\mu$c. Formula for calculation of statistical error, σ:

$$\sigma = \sqrt{A_{(2)}^2 + A_{(3)}^2} + (A_{(1)} + A_{(2)} + A_{(3)} + A_{(4)})^2 \text{ (c.p.m.)},$$

where A_E stands for the counts accumulated (in 32 min.) in the channel between $(E - 4)$ keV. and $(E + 4)$ keV.

‡ $V = \dfrac{A_N : W_N}{A_L : W_L}$

the concentration ratio observed for this group of samples represents a mean value for three individuals. In the two other groups listed, activities of lung and lymph nodes of one individual were compared. As shown in the last column but one, the cerium-144 activities found in the lymph nodes were between 1/8 and 1/3 of the activities of the lungs. Since the mass of the lymph nodes is quite small, the specific activity (concentration of radioelement) in these organs is many times greater than in the remainder of the lung. The concentration ratios calculated are given in the last column. Because of the statistical error of the measurements, the values are only approximate; but it is apparent that an increase in specific activity of one to two orders of magnitude has occurred. Rather similar values were found in the investigations cited above[3–6].

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Pituitary Effect on Synthesis of Deoxyribonucleic Acid in Regenerating Rat Liver following Whole-body X-irradiation

WHOLE-BODY X-irradiation delivered within 6 hr. of hepatectomy will inhibit the synthesis of deoxyribonucleic acid (DNA) in regenerating liver. This inhibition has been elegantly demonstrated to be a result of the failure to synthesize certain enzymes concerned with the formation of DNA[1]. The nature of this inhibition of enzyme formation is suggested by two recent reports. Myers[2] has reported that synthesis of DNA in regenerating liver is not completely inhibited following X-irradiation of liver only, and Benjamin and Yost[3] have observed that the uncoupling of oxidative phosphorylation seen in liver mitochondria following whole-body irradiation is due to a pituitary stimulation with subsequent activation of the adrenal cortical hormones. These observations suggest that this interesting and rather unusual effect of low doses of whole-body X-irradiation on synthesis of DNA in the intact animal may be due to a pituitary stimulation which ultimately results in a decreased amount of energy being available for enzyme synthesis. The possibility of a pituitary effect on synthesis of DNA in regenerating liver following whole-body X-irradiation was confirmed in the experiments reported here.

Male Sprague–Dawley rats (180–200 gm.) underwent partial hepatectomy by a standard method[4], and then were irradiated within 2 hr. of the operation. The animals were given 15 μc. radioactive phosphate intraperitoneally 3 hr. before they were killed (see Table 1 for schedule). Following killing, the livers of all animals within a group (2–3) were pooled, the DNA isolated, and the specific activity determined as suggested by Hecht and Potter[5]. All irradiated animals received 750 r. delivered by a General Electric 'Maxitron 250' operated at 30 m.amp., 250 kVp. with added filtration of 1 mm. aluminium, 0·5 mm. copper, delivering 106 r./min. at 50 cm. Shielding of animals was accomplished in a restraining box covered with 1·5 cm. lead located outside the radiation beam.

The results of these experiments are summarized in Table 1.

Table 1. SPECIFIC ACTIVITY OF DNA ISOLATED FROM REGENERATING RAT LIVER FOLLOWING VARIOUS RADIATION PROCEDURES

Procedures	Time after death (hr.)	Specific activity (c.p.m./mgm.)
Non-irradiated	18	0
Non-irradiated	22	777
Whole-body	22	0
Head only	22	0
Body only	22	38
Body only + 10 units of adrenocorticotrophic hormone	22	0
Body only + 1 unit of thyroid stimulating hormone	22	0

These experiments show that under conditions in which synthesis of DNA is active (19 hr. postoperative), 750 r. delivered either to the whole body or to the head will suppress synthesis of DNA in regenerating liver. Head shielding resulted in a markedly reduced synthesis and the administration of pituitary hormones immediately following irradiation further abolished DNA synthesis. The reciprocal experiments were also tried using commercial hypophysectomized rats but none of these animals survived the course of the experiment. The conclusion from this series of experiments is that irradiation of the head alone produced the same inhibition of DNA synthesis in regenerating liver as irradiation of the whole body, and that DNA synthesis, although reduced, was present when the head was shielded. The reduction of DNA synthesis in animals with their heads shielded may be the result of adrenal stimulation following X-irradiation.

In view of the importance of regenerating liver as a system for studying synchronous formation of DNA, these experiments serve as a reminder that contributions from other organs in modifying synthesis of DNA in liver should not be ignored. This is especially true in radiation work on synthesis of DNA as well as on population changes in 'radiation-sensitive' tissues.

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Radioprotective Effects of Reserpine and its *N*-oxide

CERTAIN amine oxides exert a protective effect against radiation injury[1,2]. Reserpine has also been shown to have this action[2]. This suggested a comparison between reserpine and its *N*-oxide. Groups of 20 *CF*–1 mice were administered various doses of the two compounds 24 hr. before X-irradiation with 600 r. (Table 1). Radiation conditions were the same as described previously[1]. Both compounds produced typical reserpine effects, sedation and ptosis, but the *N*-oxide was less active per dose. All three doses of reserpine *N*-oxide significantly increased the ST_{50} day, whereas only one dose of reserpine had this effect (Table 1). On the basis of total survival it requires twice as much reserpine as its *N*-oxide to decrease mortality by 25 per cent, and neither compound is as effective as quinoxaline di-*N*-oxide[1] or anhydroerythromycin *N*-oxide[3]. Mechanisms of action are probably different, since the reserpine compounds exert no antibiotic effects. However, they have the proper chemical structures postulated for removing oxidizing radicals[3]. Protection might be partially the result of the release of known protective compounds, adrenaline and 5-hydroxytryptamine[4]. The release of catecholamines and 5-hydroxytryptamine is essentially complete 16 hr. after reserpine administration, and the binding sites, as well as the plasma content, do not begin to contain appreciable amounts of these amines for at least 4 days[6–9]. Metabolism and excretion are also going on at this time, and in all probability the amount of such amines available for exerting a protective effect is below that necessary for such an action. On the other hand, reserpine has been found in body tissues for at least 48 hr. following a single dose[10]. Most of the reserpine was found in the tissue cells where, in the present radiation experiment, it could act as a protecting compound. The fact that reserpine and its *N*-oxide exert only a slight protective effect against

Table 1. Orally Administered Reserpine and its *N*-Oxide and Survival after X-Irradiation

Treatment	Dose (mgm./kgm.)	ST_{10}* and range	Slope and range	Mortality Final (per cent)	Days
Water control		10·0 (8·4–12·0)	1·52 (1·33–1·73)	100	28
Reserpine	10	13·8 (12·0–15·9)†	1·38 (1·24–1·54)	90	30
	15	9·1 (6·8–12·1)	1·95 (1·58–2·39)	95	30
	20	13·0 (10·0–16·9)	1·78 (1·44–2·21)	75	30
Reserpine *N*-oxide	10	15·5 (12·7–18·9)†	1·58 (1·32–1·84)	75	30
	15	13·2 (10·9–16·0)†	1·54 (1·34–1·78)	90	30
	20	13·8 (12·8–14·9)†	1·20 (1·13–1·27)	100	19

* ST_{10} day on which 50 per cent of animals are expected to be still alive.
† Differs significantly from control values. $P = 0.05$ (ref. 4).

lethal X-irradiation points out the need for continuing the search for compounds having low toxicity and greater protective effects at the cellular level.

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BIOLOGY

Requirement of Essential Fatty Acids and Avian Atherosclerosis

Although Reiser in 1950[1] claimed that chickens needed a source of essential fatty acids during growth, the same author later concluded[2] that mature hens, maintained for a full year on a fat-free diet, did not require essential fatty acids for egg production or hatchability. More recently Bieri *et al.*[3,4] showed that chicks could be grown to maturity on an essentially fat-free ration without marked deficiency symptoms and suggested that Reiser's purified chick ration may have been deficient in thiamine and vitamin A. In contrast with the chicken, exclusion of essential fatty acids from the diet of several mammals leads to a clear deficiency disease which, among more apparent external symptoms, is also characterized by an increase in liver and epidermal cholesterol and a decrease in serum cholesterol in the rat[5], and by aortic lesions in the pig[6]. Such observations lend support to the view of a possible connexion between deficiency of essential fatty acid and atherosclerosis[7]. Since atherosclerosis develops in the chicken on low-fat as well as on normal rations[8], it seemed of interest to determine if rigid exclusion of essential fatty acid from the diet would aggravate aortic lesions. At the same time more information regarding the requirement of essential fatty acids and deficiency symptoms would be obtained from a group of birds maintained continuously on a diet deficient in essential fatty acids from the day of hatching until 19 months of age.

Day-old female chicks (10 per lot) were given either fat-free (albumen-glucose) or normal, fat-containing (about 3 per cent corn oil) rations for 19 months. On the fat-free diets the birds developed less rapidly (Table 1) than on the normal ration, but were otherwise asymptomatic. The early weight differences were largely overcome after 18 months. In our opinion the extreme dryness of the fat-free ration interfered with prehension and deglutition in the birds consuming this diet. In order to improve the physical texture of the fat-free diet, starch was substituted for part of the glucose. Although this improved the texture and increased feed consumption, it was found by analysis[9] that the starch supplied 0·06 per cent dienoic acid to the ration so that the starch was again removed. Acid hydrolysis was used to determine any residual fat since conventional solvent extraction procedures were ineffective.

Table 1. Effect of the Exclusion of Essential Fatty Acids from the Diet of Chickens

	Diet free of essential fatty acids	Normal diet containing essential fatty acids
Body-weight (gm.)		
8 weeks	367 ± 16	695 ± 28
12 months	1,550 ± 74	1,773 ± 91
18 months	1,678 ± 53	1,735 ± 108
Age at first egg (weeks)	24	20
Fatty acid composition of egg lipid (percentage of fat *		
Saturated	30·8	40·9
Monoenoic	66·8	45·9
Dienoic	0·9	9·8
Trienoic	1·4	0·4
Tetraenoic	0·1	1·7
Pentaenoic	0	0·5
Hexaenoic	0	0·9
Plasma cholesterol (mgm./100 ml.)	248 ± 23	160 ± 12
Atherosclerosis		
Aorta score†	1·7 ± 0·2	2·1 ± 0·2

* From eggs collected after one full year of production.
† Of the 10 chicks started on each diet there ultimately were 5 and 8 left at the end of 19 months on the fat-free and normal diets respectively. Only non-specific causes were responsible for the deaths. For details regarding the scoring technique, see Fisher *et al.* (ref. 11).

The time of onset of egg production was delayed by one month in the birds on the fat-free diet, as shown in Table 1. Egg production was good, but sporadic, on the fat-free diet, and there was only one bird on this régime that never laid. On autopsy, however, this bird was found to have been an internal layer with an active ovary at time of killing. Egg production on the conventional ration was somewhat better. It is also worth noting that fertilized eggs from the hens on the fat-free ration hatched apparently healthy chicks.

Even after one year of egg production the eggs from the birds on the fat-free diet still contained small amounts of dienoic acid, as shown in Table 1. Even when the trace of dienoic acid (supplied by the starch which had been fed for a short time) is taken into account we cannot explain the origin of the dienoic acid in the eggs other than to suggest biosynthesis. However, Murty *et al.* recently showed that linoleic acid could not be synthesized from acetate by the laying hen[9]. Compared with the eggs from birds on the normal ration, the trienoic acid content of eggs from birds maintained on a fat-free diet is almost 3 times as high. Such elevated levels of trienoic acid in the tissue lipids have been considered an excellent indicator of the state of deficiency of essential fatty acids in the rat[10].

The plasma cholesterol values of the hens shown in Table 1 indicate a clear elevation in the fat-free versus the normal hens. By contrast, and in agreement with the observation of Horlick *et al.*[8], on a low-fat diet the visual aortic scores were actually lower in the fat-free, compared with the normal birds (Table 1).

In summary, it appears that in the chicken the exclusion of essential fatty acids from the diet does not aggravate atherogenesis even though the level of cholesterol in the blood is elevated. Moreover, no overt deficiency symptoms such as skin lesions or impaired reproductive functions were encountered.

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Anthropometric Correlations between Adult Brothers

Anthropometric measurements have been made on 32 pairs of brothers. All subjects are adult men. The average age of the younger brothers is 32·3 yr., that of older brothers, 39·4. Age differences between members of the same pair vary from 1 to 20 years. The brother–brother correlations are shown in Table 1. Some coefficients are low but, unless below 0·35, they are significant at the 5–1 per cent level. Low coefficients are to be expected because in a panmictic population a brother–brother correlation should not significantly exceed 0·50 (or 0·42 for autosomal dominant characters). Other coefficients are higher but, as for low significant correlations, with two exceptions there is no significant departure from 0·50. For head breadth and cephalic index, correlations are surprisingly high and significantly above 0·50. Such values can be expected if, instead of random mating, there is a fairly high degree of homogamy. In man, assortative mating exists primarily for body-height, secondarily for some characters correlated with stature. In our sample, fraternal correlation for body-height is low and does not differ significantly from 0·50, the limiting value compatible with panmixia. One can guess that assortative mating is directly related to some other anatomical traits, but it is hard to believe that cephalic index, which gives the strongest correlation, can be sexually attractive. A quite different explanation seems to be more credible.

Table 1. Correlations between Pairs of Adult Brothers

	This sample r	Howells's data* r
Stature	0·35	0·47
Sitting height	0·50	0·39
Trunk height	0·62	—
Vertex-suprasternale	0·64	—
Neck length	0·32	—
Upper limb length	0·15	—
Lower limb length	0·40	—
Head length	0·54	0·38
Head breadth	0·72	0·48
Head heigth	−0·11	0·49
Cephalic index	0·76	—
Minimum frontal breadth	0·34	0·47
Bizygomatic breadth	0·16	0·29
Face height	0·16	0·59
Nose height	0·27	0·51
Nose breadth	0·44	0·25
Mouth breadth	0·41	—

* Corrected figures published by J. M. Tanner (ref. 1).

Our sample does not represent a definite geographical area. As for many other samples, it is fortuitously mixed, because subjects come from different parts of the country. Two groups of fraternal pairs come from two distinct areas, the populations of which are anthropologically different. One is far more dolichocephalic than the other. In our small sample, these two groups are strong enough to increase the coefficient of correlation. The mingling of two more or less dissimilar groups—panmictic but 'allopatric'—can exaggerate fraternal correlations in a way which simulates homogamy. After all, in this case, excessively high correlations are due to a kind of assortative mating, not by choice, but by geographical isolation. Therefore, both exceptionally high fraternal correlations are not intrinsically wrong, but their numerical value should be reduced in some way.

On the whole, significant correlations are in accordance with other data. Unfortunately, so far as I know, only three series of fraternal correlations have been published, with not entirely comparable assortments of characters[1]. Seven correlations of Table 1, without corresponding values in Howells's data, have been calculated probably for the first time. In 22 pairs, the eye colour, classified as light (blue, grey) and dark (all other shades), is similar ($\chi_1^2 = 4{\cdot}57$; $P = < 0{\cdot}05$). But for hair colour there is no fraternal similarity.

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Goblet Cells in the Swim Bladder of *Ophiocephalus striatus* (Bloch)

During investigations on the mechanism of gas secretion by the gas gland epithelium in the swim bladder of teleosts, a preliminary investigation was made of the histology and histochemistry of the gas gland to identify the types of cells which are involved in the secretion of gases.

Adult *Ophiocephalus striatus* were caught as and when required and stunned by a blow on the head and the swim bladder rapidly dissected out and fixed in Zenker's, Helly's and Champy's fluids, a saturated solution of mercuric chloride in 70 per cent alcohol with 2·5 per cent potassium dichromate, a mixture of equal parts of saturated aqueous mercuric chloride and 2·5 per cent aqueous potassium dichromate, and a solution of equal volumes of 8 per cent aqueous basic

Fig. 1. Swim bladder epithelium of *Ophiocephalus striatus* (× *c.* 970). Fixed in saturated mercuric chloride with 2·5 per cent potassium dichromate and stained with Bensley's neutral gentian. Note along the border of the epithelium rounded, deeply stained cells with thick striations in the cytoplasm. The very dark bodies are blood cells

lead acetate and 16 per cent formalin. They were washed, dehydrated and embedded in paraffin as usual. Sections 2–6μ thick were stained with hæmatoxylin-eosin, Mann's stain, rapid phloxine-methylene blue, Bensley's neutral gentian and Delafield's hæmatoxylin.

These stains revealed a type of cell which is different from the main types of cells found in the swim bladder epithelium. This type of cell is found only towards the lumen of the bladder and is seen distinctly as a one-cell border in places where the cells are present in large numbers (Fig. 1). They are not seen in the depths of the glandular mass. In the region of the main glandular mass these cells are relatively less numerous but more abundant where the epithelium is thin.

The cells are usually rounded or ovoid and similar to goblet cells seen elsewhere. The nucleus is seen pushed to the base of the cell away from the lumen. In all the stains used the nucleus has taken a blue colour. Clear cytoplasm is seen just around the nucleus and above this is the condensed matter with very fine granules filling almost the entire cell. In some cells the condensed matter appeared to be crescentic. The space around these cells is clear of stain. In the rapid-phloxine methylene-blue stain the cytoplasm of the cell is stained a bright pink. In sections stained with Mann's stain these cells have taken less eosin than the main glandular mass adjacent to them. The condensed matter is stained violet with Bensley's neutral gentian, and often a clear border is present between the condensed matter and the cell wall. In some cells, probably spent ones, there can be seen violet round bodies, while in many others violet striations along the long axis are seen in addition. In the slides stained with hæmatoxylin-eosin, only a slight difference is seen in the staining between these cells and the rest of the gland cells.

These cells resemble the goblet cells seen in the epithelial lining of the intestines. Hence some sections were stained in 0·1 per cent toluidine blue in 1 per cent alcohol and others in 0·1 per cent toluidine blue in 30 per cent alcohol and some others in 0·2 per cent Ehrlich thionin for mucoproteins. There was no metachromasia in the cells of the swim bladder epithelium while there was well-marked metachromatic staining of the intestinal goblet cells which was more pronounced with the dye made in 30 per cent alcohol and still better in the thionin. Cells similar to those observed have not been described by previous workers on the fish swim bladder. George[1], who has studied the swim bladder epithelium of four species of *Ophiocephalus*, fails to mention their occurrence. Such cells have, however, been described in the alimentary tract of *Labeo* by Girgis[2] and in the epithelium of the accessory respiratory organs of *Clarias*, including the air chamber, by Moussa[3]. Their function is that of secreting mucin, and so it seems quite likely that the cells seen in the swim bladder also have a mucus-secreting function. It is evident, however, that there is some qualitative difference in the products of secretion produced by the cells described here and those occurring in the intestinal mucosa.

In the swim bladder of *Gadus morhua* "a copius secretion of a viscid, slimy opaque material" has been described by Vincents and Barnes[4]. Fange[5] worked on this material and he says "that very probably the secretory product discovered by Vincents and Barnes in some way originates from vacuoles of the gas gland cells". He has not, however, identified any particular type of cell causing this secretion. The presence of a slimy secretion in the lumen of the swim bladder has been reported by many other workers also. Scholander[6] notes that the bubbles of gas are secreted into the mucus covering the gland. The mucus may, therefore, have a very important function with reference to gas secretion. It is also quite likely that there has been some confusion in the material examined by these workers as they think that these secretions are in the nature of myelin and related to the secretory vacuoles. Vacuoles and granules have also been observed in the gas gland of this fish in the cytoplasm of the main type of cells; but no vacuoles have been seen in the cells described here. The vacuoles of the gland cells are probably related to the gas-secreting activity of the gland. Thus the cells described here seem to be different in function and to be responsible for a mucoid secretion. Further work is progressing under the supervision of Prof. C. M. Francis, of this College.

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Natural Occurrence of *Leptospira icterohæmorrhagiæ* in the Eastern Grey Fox and the Eastern Raccoon

Previous investigations of wild life in the United States have established the grey fox and the raccoon as natural hosts of leptospires. *Leptospira ballum*[1], *L. australis A*[2], and *L grippotyphosa*[2] have been isolated from the grey fox. *Leptospira ballum*[1], *L. pomona*[1], *L. australis A*[2], *L. grippotyphosa*[2], *L. autumnalis*[4], and *L. mini-Georgia*[5] have been isolated from the raccoon.

This communication concerns the first isolations in the United States of *L. icterohæmorrhagiæ* from the

Table 1. LEPTOSPIRAL ISOLATIONS FROM KIDNEY SUSPENSIONS

Animal	Day growth detected	Mediums supporting growth
Grey fox—38	Day 12 post-inoculated	Semi-solid Fletcher—horse; semi-solid Chang's—horse
Raccoon—7	Day 5 post-inoculated	Semi-solid Fletcher—horse
Raccoon—76	Day 12 post-inoculated	Semi-solid Chang's—horse and rabbit; 10^{-4} diluted semi-solid Fletcher—rabbit
Raccoon—80	Day 8 post-inoculated	Semi-solid Fletcher—horse; semi-solid Chang's—horse; 10^{-3} and 10^{-4} diluted semi-solid Fletcher—rabbit

eastern grey fox and the eastern raccoon. The isolations were made during the course of an epizootiological investigation of leptospirosis in Pennsylvania wild-life.

The species of wild-life investigated were caught in No. 2 coil spring steel traps. Specimens were removed alive from the traps and transported to the School of Veterinary Medicine, University of Pennsylvania. On arrival at the Laboratory, the animals were asphyxiated in a carbon monoxide chamber. Blood specimens for serological testing were collected and a portion of one kidney was removed aseptically from each animal.

Each kidney specimen was ground with sterile mortar and pestle and diluted to a 10 per cent suspension with Stuart's liquid medium base (Difco). One to three drops of the suspension were inoculated into one tube of each of the following media: Fletcher's semi-solid medium (Difco) with 10 per cent rabbit serum, Fletcher's semi-solid medium with 15 per cent horse serum, Chang's semi-solid medium with 15 per cent horse serum, and Stuart's semi-solid medium[7] with 10 per cent rabbit serum.

Serial ten-fold dilutions of the kidney suspension were made, with Stuart's liquid medium base, to approximately 10^{-1} to 10^{-5} final dilutions. One to two drops of each dilution were inoculated into a tube of Fletcher's semi-solid medium with 10 per cent rabbit serum. All inoculated mediums were incubated at 29° C. and examined by dark-field microscopy at 10–14-day intervals. Culture results are summarized in Table 1.

Sub-cultures of media containing growth of Leptospires were made into Fletcher's semi-solid medium with 10 per cent rabbit serum and Stuart's liquid medium with 10 per cent rabbit serum. Sub-cultures of each isolate were sent to the World Health Organization Reference Laboratory for Leptospirosis, Walter Reed Army Medical Center, Washington, D.C., and to the Leptospirosis Unit, Animal Disease Eradication Division, Ames, Iowa, where they were identified as *L. icterohæmorrhagiæ*.

Microscopic agglutination tests were conducted on serum specimens collected from each animal at the time of culturing using an antigen bank of eleven leptospiral serotypes: *L. bataviae*, *L. pomona*, *L. autumnalis*, *L. ballum*, *L. canicola*, *L. icterohæmorrhagiæ*, *L. alexi*, *L. grippotyphosa*, *L. australis A*, *L. sejroe* and *L. hyos*. Test results are summarized in Table 2.

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Synergid Haustoria of *Quinchamalium chilense* Lam.

DECAISNE[1] pointed out that in *Santalum album*, *Nanodea*, *Myoschilos*, *Osyris* and more obscurely in *Quinchamalium*, the tip of the embryo sac extends beyond the ovule into the ovarian cavity. The present account is based on an investigation of *Quinchamalium chilense*, a native of the South American Andes.

The ovary is inferior with a free-central placental column, bearing three hemianatropous, unitegmic ovules, the nucellus being reduced to one or two epidermal cells capping the megaspore mother cell. The thick integument does not grow beyond the nucellus and thus a micropyle is not formed. The embryo sac is of the Polygonum type and extends beyond the ovular epidermis at the 4-nucleate stage. At maturity it comprises the egg apparatus, two polar, and three antipodal nuclei. The latter are separated from the rest of the embryo sac by a wall, but do not become organized into individual cells.

In most of the Santalaceae, the synergids are inconspicuous, have small nuclei, and degenerate before or soon after fertilization. In *Q. chilense*, on the contrary, they are unusually large and pear-shaped with prominent nuclei. Even in unpollinated flowers they protrude beyond the embryo sac (Fig. 1*a*) and eventually extremely long (approximately 1,200μ) tubular structures reaching up to one-third the length of the style are formed (Fig. 1*b*). These are densely cytoplasmic and sometimes persist until the endosperm has become quite massive. Dahlgren[2] has recorded that in some members of the Compositae, namely, *Calendula arvensis*, *Mutisia candolleana* and *Ursinia anthemoides*, the tips of the synergids extend into the micropyle and even beyond it, sometimes reaching as far as the funiculus. Paliwal's[3] observation that in *Santalum album* dichotomously branched synergid haustoria develop after fertilization has been contradicted by Bhatnagar[4]. The

Table 2. MICROSCOPIC AGGLUTINATION TITRES OF SERUM SAMPLES OBTAINED AT THE SAME TIME AS KIDNEYS WERE CULTURED

Animal	Leptospiral serotypes										
	Bat.	*Pom.*	*Autum.*	*Bal.*	*Canicola*	*Ictero.*	*Alexi*	*Grippo.*	*Aust. A*	*Sejroe*	*Hyos*
Grey fox-38	—	—	—	—	—	100	—	—	—	trace	—
Raccoon—7	—	100	trace	—	—	—	trace	trace	trace	trace	trace
Raccoon—76	—	—	—	—	—	400	—	—	trace	—	—
Raccoon—80	—	—	—	—	trace	400	—	—	—	—	—

XUM

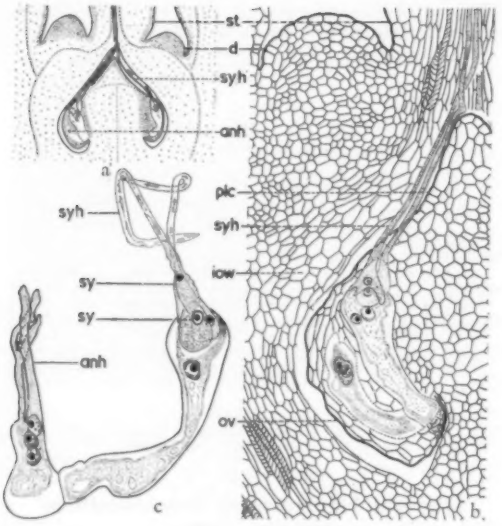

Fig. 1. *a*, Longisection of base of flower showing floral parts and extension of synergid and antipodal haustoria (× 40); *b*, semi-diagrammatic enlargement of 1*a* to show the details of embryo sac in relation to ovary and style (× 124); *c*, whole mount of embryo sac showing the synergid and antipodal haustoria (× 262). anh, Antipodal haustorium; d, disk; iow, inner ovary wall; ov, ovule; plc, placental column; st, style; sy, synergid; syh, synergid haustorium

latter author has pointed out that in this plant the synergids degenerate soon after fertilization and that Paliwal had mistaken the persistent pollen tubes which remain adhering to the embryo sac (see also Griffith[5,6]) for synergid haustoria. Thus, *Quinchamalium* has perhaps the longest synergid haustoria so far known in any angiosperm.

In addition to very long and conspicuous synergid haustoria *Quinchamalium chilense* also shows a much-branched antipodal haustorium. As mentioned earlier, the antipodal nuclei do not become organized into cells. Instead, they enlarge, become hypertrophied and multinucleolate and may even divide. Later the chalazal end of the embryo sac extends as far as the placental column and branches profusely (Fig. 1c). These branches ramify into the placental tissue in the vicinity of the vascular supply. In the Santalaceae an extension of the chalazal end of the embryo sac into a cæcum leaving the antipodal cells *in situ* is a common feature. In *Quinchamalium* the antipodal nuclei are carried at the tip of the haustorium until it branches (Fig. 1c). The activity of the synergid and antipodal haustoria declines with the progressive development of the endosperm.

The embryology of other species of *Quinchamalium* and allied genera, namely, *Arjona* and *Myoschilos*, is as yet unknown and it would be worth while to investigate them to ascertain if prominent synergid haustoria develop in these plants also.

I shall be grateful if botanists could help me in procuring the preserved materials of all stages of buds, flowers and fruits of different species of *Arjona* and *Myoschilos*.

I am indebted to Dr. B. M. Johri and Prof. P. Maheshwari for guidance. Thanks are also due to Dr. S. P. Bhatnagar for comments, to Mr. V. Garcia, University of Buenos Aires, Argentina, now working at the University of Delhi, for providing the material, and to the Council of Scientific and Industrial Research for financial assistance.

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Relation between Organophosphorus-Resistance and Non-Diapause in Spider Mites

As has been shown by Lees[1], the females of *Tetranychus urticae* enter into diapause under the influence of a short-day treatment during their development. High temperatures tend to prevent diapause even if the photoperiod is short.

An investigation into the diapause-pattern of several spider mite populations originating from places in different countries (the Netherlands, Belgium and Germany) proved that the critical area of the diapause-pattern of seven populations was significantly smaller than may be expected. Only four populations showed a diapause-pattern in accordance with the data of Lees.

In work on the susceptibility of the populations to organophosphorus compounds it appeared that the seven populations with the deviating diapause-pattern were organophosphorus-resistant; the four

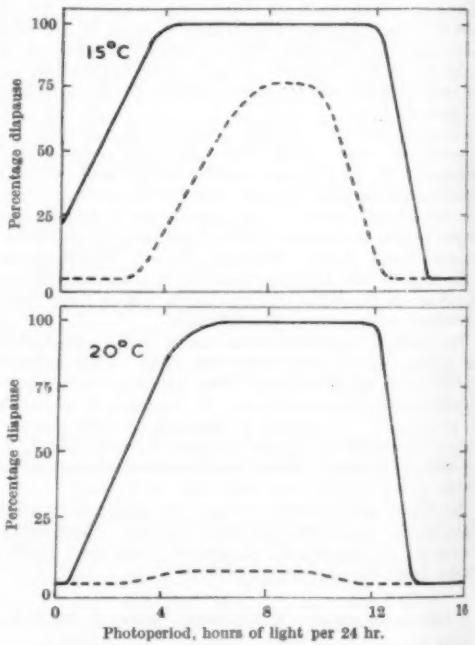

Fig. 1. The effect of photoperiod on the incidence of diapause in two populations of *Tetranychus urticae*. The dotted line represents an organophosphorus-resistant population, the continuous line a susceptible population

populations with a normal diapause-pattern showed a high susceptibility to organophosphorus compounds.

Fig. 1 shows the difference in diapause-pattern between a susceptible and an organophosphorus-resistant population. At 20° C. a régime of short photoperiods evoked only a small percentage of diapause forms in the resistant population. At 15° C. resistant mites entered into diapause, but the percentage of diapause forms was significantly lower with the resistant population than with the susceptible one.

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Effect of Copper Deficiency in White Clover on Nitrogen Fixation

In view of a recent report by Hallsworth *et al.*[1] that copper stimulates nitrogen fixation by subterranean clover (*Trifolium subterraneum*), the following evidence from a field trial is presented as indicating a similar function of copper in nitrogen fixation by white clover (*T. repens*).

White clover was dissected from mixed herbage samples taken on November 27, 1956, from a rates of copper trial conducted by one of us (F. H. v. d. E.) on a pasture recently established on raw peat on the Moanatuatua swamp. The samples were analysed for copper and total nitrogen contents.

Many clover plants in the control plots showed characteristic copper deficiency symptoms—die-back with bleaching of the margins and rolling and collapse of the leaflets. The samples analysed were apparently healthy whole leaves (leaflets plus petioles).

Table 1. Yields of Mixed Herbage and Copper- and Nitrogen-Levels in White Clover

Treatment	Dry matter yield (lb. per acre) (Spring 1956)	Copper (p.p.m. in dry matter)	Nitrogen (percentage in dry matter)
Control	2,090	2·5	4·25
5 lb. Bluestone	3,330	3·6	4·88
10 lb. Bluestone	3,410	4·0	4·94
20 lb. Bluestone	3,540	6·6	5·05
40 lb. Bluestone	3,620	7·2	5·00
80 lb. Bluestone	3,520	8·2	5·03
Significant 5% differences 1%	350 470	0·78 1·05	0·16 0·21

The copper treatments resulted not only in increased growth of white clover and elimination of deficiency symptoms, but also in significantly higher concentrations of total nitrogen. Incubation tests of the peat soil with copper additions failed to demonstrate any increase in mineral nitrogen-levels. The clover nitrogen-levels in the controls were relatively low for succulent spring growth under local conditions, but normal in the copper-treated plants. The presence of copper deficiency symptoms together with low nitrogen- and very low copper-levels suggests that the increases in nitrogen concentrations in the clovers were due to a specific effect of copper on nitrogen fixation by white clover.

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Limitations of the Periodic Acid–Schiff Technique for the Demonstration of Stages of *Eimeria* in Tissues

In a recent communication, Jennings[1] suggested that the periodic acid–Schiff technique is useful for the demonstration of all stages in the life-cycles of four species of coccidia occurring in the intestine of the fowl. These species were *Eimeria acervulina*, *E. maxima*, *E. necatrix* and *E. tenella*.

The periodic acid–Schiff technique was first applied to *Eimeria* by Lillie[2], who obtained positive reactions in the cytoplasm of oocysts of *E. stiedae* from the rabbit. More recently, this technique was used by Cheissin[3] on *E. magna*, *E. media* and *E. intestinalis* from the rabbit, Pattillo and Becker[4] on *E. acervulina* and *E. brunetti* from fowls, Gill and Ray[5] and Tsumoda and Itikawa[6] on *E. tenella* from fowls. These authors all failed to obtain positive reactions by the periodic acid–Schiff technique with some stages of these life-cycles. Cheissin found that isolated microgametes were negative and that microgametocytes gave only an insignificant reaction. Pattillo and Becker obtained no positive reactions using the Hotchkiss[7] periodic acid–Schiff technique with the microgametocytes and schizonts of both *E. acervulina* and *E. brunetti*, although the merozoites of *E. acervulina* gave a weak reaction. Developing macrogametocytes were often negative.

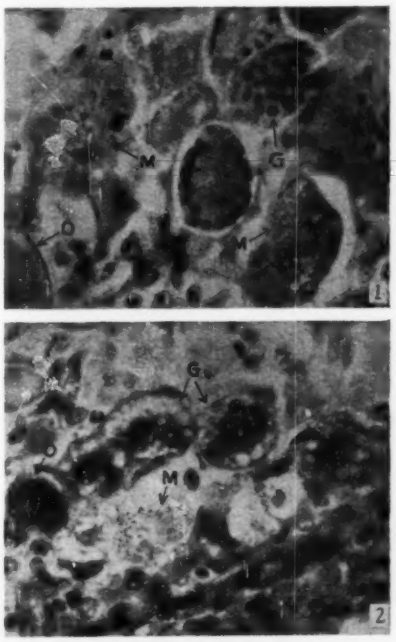

Fig. 1. Section of small intestine infected with *E. maxima* and fixed in formol saline; stained by Hotchkiss periodic acid–Schiff technique and counter-stained with hæmalum. Note the intense staining of the 'plastic granules' (*G*) in the macrogametes and oocyst wall (*O*). The microgametocytes and microgametes (*M*) have stained with the hæmalum but not with the periodic acid–Schiff reagent. (× 525)

Fig. 2. Section of small intestine infected with *E. maxima* and fixed with Bouin's fluid; stained by Hotchkiss periodic acid–Schiff technique and counter-stained with hæmalum. Note the lack of preservation of the plastic granules in the macrogametes (*G*); the microgametocytes and microgametes (*M*) have stained with the hæmalum, but not with the periodic acid–Schiff reagent. (× 525)

In our experience, the invading sporozoites and merozoites of *E. tenella* give only weak reactions and consequently the technique is of little value in demonstrating these stages in tissues. Long and Rootes[3], using the Hotchkiss periodic acid–Schiff technique, showed that the reactions of the prominent so-called 'plastic granules' of the macrogametes depend on the type of fixative used (see Figs. 1 and 2). According to Pattillo and Becker, these granules probably consist of a protein–carbohydrate complex, which is unaffected by pre-treatment with saliva or α-amylase. Fixation with Bouin's fluid fails to preserve these granules, and negative results are obtained with the periodic acid–Schiff technique although there is no interference with the staining of the glycogen in the cytoplasm. For these reasons the periodic acid–Schiff reaction is not an appropriate technique for the demonstration of all stages of the life-cycles of *Eimeria*, and when used on sections of very heavily parasitized intestinal tissue, large amounts of mucus giving a positive reaction with the periodic acid–Schiff technique may mask the parasites. The same difficulty may be encountered when the technique is applied to sections of rabbit liver containing trophozoites and small stages of the asexual and sexual cycles of *E. stiedae*, because of the possible masking effect of the stained liver glycogen.

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CYTOLOGY

Identification of the Chromosome Complements of New-born and Adult Living Mice

Chromosome abnormalities similar to those known in man are now being found in mice[1]. Identification of the chromosome complement of these mice in cells from bone marrow[2] or corneal epithelium[3] involved the death of the animals. The advantage in identifying the chromosome complement of living mice is obvious, and the present communication describes techniques to achieve this in new-born and in adult mice, chiefly by the use of primary outgrowths of cells from pieces of tissue cultured *in vitro*.

The chromosome complement of new-born mice aged 1–3 days has been identified in cells from small pieces of tail. Loss of their tail-end does not obviously affect the development of these mice. Attempts to obtain cells in mitosis for chromosome counts directly from the tail-pieces were not uniformly successful, hence the pieces have been cultured *in vitro*. Before removal from the mouse, the tail-ends are washed in a mixture of alcohol and ether; this serves as a partial anæsthetic and to clean the tails. The excised tail-ends are then washed in Gey's solution containing mycostatin, penicillin and streptomycin, cut into four or five small pieces, and mounted separately in tiny plasma clots on a 3/4 in. cover-slip. The cover-slip is inverted in a cavity cell, and growth medium is added. Antibiotics and mycostatin are necessary to keep down bacteria and fungi respectively. Initially, Gey's solution containing 15 per cent calf serum, 2 per cent chick embryo extract, and 0·5 per cent lactalbumin hydrolysate was used as the growth medium, but this was later superseded by medium 199 (Glaxo Laboratories), plus 15 per cent calf serum. The medium is changed every other day, and all cavity cells are gassed with 5 per cent carbon dioxide.

Cells emerge from the grafts within one or two days (Fig. 1). After 4–5 days, the cell monolayer in many of the cultures is ready for cytological preparation. The small pieces of tail, still easily recognizable, are gently pulled off the cover-slip with least disturbance to the cell monolayer, and are re-embedded in tiny plasma clots on another cover-slip to serve as a reserve if needed. The cover-slip containing the cell monolayer is then re-inverted into the growth solution and treated for chromosome processing in a manner similar to that described in ref. 4: 'Colcemid' (Ciba Pharmaceuticals) at a concentration of 0·25–0·50 μgm./ml. for 2 hr., hypotonic saline for 15 min., and fixation in 45 per cent acetic acid. In practice, after removal of the growth medium 'Colcemid' mixture, 1 ml. saline is placed in the cavity cell, 2·5 ml. distilled water is added dropwise, and the acetic acid added slowly 15 min. later. This concentration of hypotonic saline, and the gradual addition of water and fixative, were found to give good spreading of the chromosomes with minimal cell breakage. After fixation, the cells were dried in air and stained by the Feulgen technique.

Mitoses are found in the great majority of the preparations. The clarity of many mitoses is sufficient to count the chromosomes easily (Fig. 2), and more than thirty of them can be selected in some cultures. If this number is not available, or if more are required, the reserve culture is available a few days later. The mitotic index is especially high in cultures fixed 10–11 hr. after change of growth medium. Details of the counts on mitoses in six tails are given in Table 1. Almost all were diploid; a few were found with less than the diploid number, and were presumably a result of cell breakage. The technique obviously

Fig. 1. Growth from a piece of tail after 3 days in culture. (× 22)

Fig. 2. Diploid mitosis from a tail culture. (× 756)

permits a fairly rapid identification of the chromosome complement of new-born mice, and twenty-two such mice have recently been examined here using an arbitrary limit of twelve clear mitoses for classification. Thirteen were classified within 5 days, six others within 7 days, and two more after 10 days; the last culture was lost through bacterial contamination.

Table 1. Chromosome Counts on Cells in Outgrowths from Tail-tip and Ear-clip Cultures

Tissue	No. of mitoses examined	Chromosome counts 31	33	39	40
Tail	68	1		2	65
Ear	45		1	1	43

Table 2. Growth from Ear Cultures

Ear tissue	Proportion of successful cultures after 12 days	Mean interval (days) until: First appearance of fibroblasts	Ready for processing
Normal	7/10	7·4 ± 0·3	14·5 ± 0·8
Regenerating for 2 days	13/13	3·6 ± 0·2	9·6 ± 0·6
Regenerating for 4 days	11/12	3·4 ± 0·3	10·2 ± 0·4

The chromosomes of adult mice were also counted in cells grown *in vitro*. Mitotic cells can be obtained directly from mice by partial splenectomy, but such an operation is often undesirable. Pieces of skin are not very suitable for obtaining cell outgrowths; growth is very slow or absent, and bacterial and fungal infections are frequent. Small pieces clipped from the ears produce a better growth. The most successful method is to make a small cut in the ear of the mouse and, 2 or 4 days later, remove small pieces containing the regenerating tissue. Cells now emigrate from the ear tissue much sooner (Table 2), and the cell monolayer can be processed for chromosome counts after approximately 10–15 days. Details of the counts made on four ear cultures are given in Table 2. The technique clearly serves to obtain an indication of the chromosome complement of the adult mouse with the minimum of discomfort to the animal.

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GENETICS

A Heterocaryon possessing Haploid and Diploid Nuclei

In general, a heterocaryon between a white and a yellow mutant of *Aspergillus* fungi gives rise to white, yellow, and green progeny. It was found recently, however, that five heterocaryons produced between two of the seven colour mutants of *A. sojae* strain *K* could give brown progeny besides the white, yellow, and green. Evidence that the brown strain appears to be a heterocaryon possessing haploid and diploid nuclei in a common cytoplasm is to be described.

Among the five heterocaryons, a heterocaryon between a white histidineless mutant and a yellow leucineless mutant was investigated extensively. The heterocaryon was produced by the method reported in ref. 1. When conidia of this heterocaryon were plated on minimal medium (Czapek agar), there appeared four kinds of colonies, namely, white 12, brown 6, green 10, and heterocaryotic colonies 4,410. Eight of the heterocaryotic colonies had brown sectors.

A conidial suspension prepared from a whole brown colony, in which more than 90 per cent of conidia were single, was spread on complete medium (Koji extract agar), and the conidial colour and nutritional requirement of each colony were examined after one week. In approximately one thousand colonies, 84 per cent were yellow, 13 per cent brown, and 3 per cent green. Using one of the brown colonies thus obtained, plating was done again on the complete medium. Results are shown in Table 1 together with the results of the third experiment. It is noteworthy that no white colony was found among the conidia of the brown strains. In addition, the yellow colonies were dependent on leucine and the brown and the green colonies were prototrophic. In contrast with this, for normal heterocaryons there was no green colony, so far as was tested, although they gave white, yellow, and heterocaryotic colonies (Table 1).

Table 1. Pattern of Segregation of the Brown Strains and Normal Heterocaryons

No. of transfer	Brown strain Segregation ratios (per cent) *W*	*Y*	*B*	*G*	No. of colonies examined	Normal heterocaryon Segregation ratios (per cent) *W*	*Y*	*X*	*G*	No. of colonies examined
1	0	84	13	3	1,100	44	43	13	0	1,680
2	0	88	9	3	1,010	41	48	11	0	986
3	0	87	12	1	1,166	40	50	10	0	802

W, White histidineless; *Y*, yellow leucineless; *X*, heterocaryotic prototroph; *G*, green prototroph; and *B*, brown prototroph.

In order to estimate ploidy of the yellow and the green segregants, numbers of nuclei/conidium were examined by the method described in ref. 2. Results were that the yellow conidium contains on the average 3·5 nuclei and the green conidium 1·7. These values approximate to those in a haploid (3·5) and a heterozygous diploid conidium (1·6) which was produced by the authentic method[2,4]. Moreover, the yellow clone was stable, and the green clone gave white and yellow progeny after a long cultivation. The appearance of white progeny from the green strain might be due to either somatic recombination or reduction[5]. It is concluded, therefore, that the nuclei in yellow conidia are haploid and the nuclei in green conidia diploid.

It is known that a white haploid nucleus and a yellow haploid nucleus in a heterocaryotic cell can conjugate under natural conditions to form a hetero-

zygous diploid nucleus which develops green colour. In the heterocaryon described before (the original heterocaryon), it seems that the diploid nuclei are seldom segregated and transmitted to progeny together with the yellow nuclei. The resulting progeny are brown. Because a single conidium of the brown strain gives rise to yellow and green progeny, the conidium is considered to be a heterocaryon possessing both haploid and diploid nuclei. The average number of nuclei in a brown conidium is about 3·0.

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ANTHROPOLOGY

Possible Origin of the Use of Fire by Early Man

Though many animals can become accustomed to the presence of fire, man alone has learned to produce, to maintain and to control it. However, this achievement is not peculiar to *Homo sapiens*. Fire was known also to *Homo neanderthalensis* and *Pithecanthropus pekinensis*[1]. From the study of fire-myths and the cultures of primitive races, it is usually presumed that fire was first obtained from such natural sources as volcanoes, bush fires, lightning, sparks struck from stones, or dry branches rubbing together in the wind[2–5]. Myths, however, are not necessarily reliable as guides to the distant past, while the reaction of animals, even of modern man, to volcanoes and forest fires is one of terror. Even when fear has been mastered, the practical difficulties of obtaining fire from these sources are still immense. Natural production of fire by friction or percussion is too rare to be readily observed by members of a small and scattered population.

An alternative to present theories is that use of fire itself is secondary to use of heat derived from bacterial decomposition of plant material. The heat produced by a haystack or compost heap is a matter of common knowledge. This heat may well become great enough to result in fire. Since many animals use as beds piled and trampled grasses, early man may well have slept in a similar manner. Individuals leading a purely nomadic existence would not use their bedding heaps sufficiently long for the warmth of decay to become apparent, but so soon as a more settled mode of life was adopted bacterial decay of the bedding could become important. Accumulation of sun-dried vegetation in a bed, perhaps a communal one, could lead to the 'compost heap' situation, presenting man with a small-scale source of heat. At first this would merely increase the temperature of his bed; later it might lead to the idea of the peat fire or even of earth-oven cooking. Occasionally, no doubt, such beds would burst into flame, providing at once the source and the idea of a blazing fire. On this theory, other means of fire-production can be regarded as being developed at a much later period, either from observation of natural events or as a by-product of chipping and grinding processes in toolmaking industries.

There can be no direct evidence for any theory of the origin of the use of fire, but it seems not unreasonable to regard the awe-inspiring character of natural fires and the rarity of small-scale fire production in Nature as militating against acceptance of present theories. In contrast, heat or flame produced by the method here suggested would be, at most, only mildly startling, while the care accorded by some primitive races to their existing fires could be interpreted as deriving from a period when an active compost heap was a most precious family possession. The 'compost heap' theory would also allow for widespread discovery of the use of fire by early man, even in regions where natural sources of fire were not available.

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PSYCHOLOGY

Validity of Prediction based on Cross-Sectional Analysis

Cross-sectional analysis, by means of which is investigated the behaviour of a cross-section of the population at a given point in time, is a convenient method in many fields of research where age or maturational differences are of interest. Implicit in the findings of such investigations are predictions about the future behaviour of the groups concerned. Such predictions are, however, based on the assumption that the behavioural differences between groups are due to the age differences involved, and that future age changes will bring about similar behavioural differences. The fallibility of such predictions in the field of demography has been pointed out[1]. This investigation is aimed at checking similar findings in the field of absence behaviour in an industrial situation.

The absence records of a group of 140 continuous service men engaged on manual work in an engineering firm during the period 1949–58 formed the material of the investigation. The sample was divided into four age-groups, each covering an approximate 10-yr. span, so that the median age of one group at the end of the period was approximately equal to that of the next oldest group at the beginning of the period. The records for each group were first analysed cross-sectionally for a 2-yr. period 1949–50, and the same groups were then followed longitudinally for a further 8 years. Two measures of absence were used in the analysis: (*a*) the number of occasions of absence, and (*b*) the average length of absences. The data were divided into five 2-yr. periods. The results for the first and last of these periods are summarized in Tables 1 and 2.

For the length of certified sickness absence (Table 2), the cross-sectional analysis based on the 1949–50 data shows a sharp increase in the length of absence for the oldest group. This agrees with the findings of previous investigators, for example, ref. 2. The prediction from this finding would be that, as age increased, group 3 would show a similar increase in length of sickness absence, and an examination of the

Table 1. Frequency of Absence for Reasons other than Sickness

Age group	No. in group	Median age at 1/1/49	1949–50 Average No. of absences per man	1949–50 No. and percentage of men with 0 absences	1957–58 Average No. of absences per man	1957–58 No. and percentage of men with 0 absences
1	20	23	2·35	3 (15)	2·75	3 (15)
2	51	31	1·61	16 (31)	1·71	18 (35)
3	34	40	1·18	18 (53)	1·71	14 (41)
4	35	51	1·63	15 (43)	1·40	15 (43)
All groups	140	35	1·61	52 (37)	1·8	50 (36)

Table 2. Length of Certified Sickness Absences

Age group	No. in group	Median age at 1/1/49	1949–50 Average length of absence (days)	1949–50 Percentage of absences lasting more than 2 weeks	1957–58 Average length of absence (days)	1957–58 Percentage of absences lasting more than 2 weeks
1	20	23	7·43	14	3·83	0
2	51	31	7·65	18	7·47	13
3	34	40	7·82	18	13·12	53
4	35	51	14·22	67	12·64	55
All groups	140	35	9·9	34	10·9	41

data for the end of the period (1957–58) shows that such an increase has, in fact, occurred. In this case the longitudinal method supports the findings of the cross-sectional method, making it probable that this is a true ageing effect.

In the case of frequency of absence (Table 1) this is not so. The cross-sectional analysis (1949–50) shows the youngest group to have a frequency of absence for reasons other than sickness higher than the other groups. Similar findings by other investigators are reported[2]. On this basis one would expect their absences to become less frequent as they grew older, but the data for the end of the period show that this has not happened and that their absence frequency has, in fact, increased relative to the average. The higher absence frequency of this group seems to be a continuing characteristic, independent of age.

The conflict of evidence arising from the use of these two methods indicates the need for greater caution in the interpretation of the results of cross-sectional investigations. The differences shown by this method may be due to the age differences involved, but the possibility that other factors are operating must also be borne in mind.

This work will be published in greater detail in *Occupational Psychology*.

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Role of Experience in Misreaching produced by Visual Cortex Lesions

When the macular projection area—that part of the visual striate cortex to which the macular region of the retina projects—is removed in monkeys a characteristic symptom can be demonstrated. The animal frequently misreaches for small pieces of food when they are presented to him on a flat surface[1,2]. The error involved may be as much as three inches, and two inches is common. It is the direction of the object, rather than the distance, which is usually gauged incorrectly by the animal; that is, his fingers fall to the sides of the object rather than beyond or in front of it. The direction of the error appears to depend primarily on which hand is used, misreaching to the left tending to occur when the left hand is used and misreaching to the right when the right hand is used. The position of the food relative to the animal's body is also important. This type of behaviour is often called 'past-pointing'; but since the error tends to be one of direction rather than distance, and also because past-pointing is also used to refer to vestibular or cerebellar derangement, we prefer to use the term 'misreaching'.

Misreaching is easily demonstrated during the first few days after operation. It declines, and almost invariably disappears within ten days. Afterwards, operated animals are as adept as normal animals at detecting and picking up small objects.

It has never been shown whether practice is necessary for this recovery to occur or whether it is the result of a spontaneous re-organization of the visual system after part of it has been damaged. The latter hypothesis might seem rather improbable were it not for the fact that we now know that the rhesus monkey is not blind in the centre of its visual field after this operation, although this region is less efficient than in the normal animal[3]. Whichever hypothesis is correct, it is interesting to contrast the high degree of plasticity in such monkeys with the lack of correction in orientation after eye rotation or similar alterations in Amphibia[4].

In order to distinguish between these two views about the recovery process—spontaneous recovery or practice—an animal was kept in total darkness for ten days after the macular projection area had been removed; he was then tested for misreaching. The result was clear. The animal misreached in exactly the same manner and for the same length of time as previous animals which had been tested without a delay after surgery. A control animal which was kept in the dark for 10 days showed no misreaching when it emerged. These statements are based on daily observations made in an experimental situation which permits quantitative estimates of misreaching from ciné film records.

It is concluded that, although the cause of misreaching is still not perfectly clear, recovery depends on experience in the light. It cannot be said without further experimental work whether mere exposure to the light is sufficient, or whether specific practice in reaching for objects is necessary. The latter appears more likely in view of recent work on the recovery of misreaching by human subjects wearing prisms[5].

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MATHEMATICS

Equation of Motion in Five Space

THERE exist many models for the description of the gravitational and electromagnetic field. Perhaps the most successful formalism developed is still that of Kaluza[1], with notable improvements by Bergmann[2] since it reproduces exactly the classic equations of the electromagnetic field with gravity. However, there still remained the well-known difficulties associated with the classic treatment of Nature so that generalizations which lead to substantially different equations were made in the hope that there could be included within the new frameworks an adequate theory encompassing quantum-phenomena as well. These hopes have not been realized; but nevertheless it is most difficult to relinquish a theory which by and large has been subject to confirmation—quite strikingly in recent times using techniques based on the Mössbauer effect[3]. In addition to numerous verifications of the original version of the theory, Einstein, Infeld and Hoffmann[4] have shown that there exists a most æsthetic feature, namely, that the field equations themselves determine the classic equations of motion of 'singularities' or 'particles' in the field. Thus it is not necessary to supplement the field equations with ponderomotive equations.

It seems to be of some interest to investigate the equations of motion in a five-dimensional setting to examine departures from the usual results. I will assume that the additional dimension is space-like and take for the field equations:

$$R_{\mu\nu} - g_{\mu\nu}R/2 = 0 \qquad (1)$$
$$\mu,\nu = 0, 1, 2, 3, 4$$

where $g_{\mu\nu}$ is the metric tensor, $R_{\mu\nu}$ the Riemann-Christoffel curvature tensor and R its contraction. '0' indices will be considered temporal, the others spatial with the '4' index reserved for the additional dimension. Now if we seek approximate solutions of the field equations corresponding as closely as possible to the four-dimensional case it is found on reckoning differentiation with respect to X_4 as leading to quantities of the same order of smallness as differentiation with respect to $X_0(= ct)$, and then proceeding in much the same fashion as in reference 2 and 4 'co-ordinates' of the 'particles' will involve X_4 as well as X_0, which would imply that the equations of motion for the position of the 'particles' will be partial differential equations rather than total differential equations. In addition to a field, which, in view of the Kaluza theory, may be interpreted as that arising from a charged 'particle,' there arises another which I make no attempt to interpret here.

For purposes of comparison let us record the results of the calculations for the metric tensors to that order essential to obtain the Newtonian approximation. These are:

$$g_{00} = 1 - c^{-2}\sum_j((12\varkappa M_j + 6\varkappa P_j)/13)V_j$$
$$g_{0s} = (6\varkappa/13)c^{-3}\sum_j(3M_j\partial\xi_j^s/\partial t - (13/2\varkappa)^{1/2}(cQ_j)\partial\xi_j^s/\partial X^4)V_j$$
$$g_{4s} = (6\varkappa/13)c^{-3}\sum_j((13/2\varkappa)^{1/2}Q_j\partial\xi_j^s/\partial t - 3P_jc\partial\xi_j^s/\partial X^4)V_j \qquad (2)$$
$$g_{40} = -\,6c^{-2}(\varkappa/26)^{1/2}\sum_j Q_jV_j$$
$$s = 1, 2, 3$$

where

$$V_j = ((X^s - \xi_j^s)(X^s - \xi_j^s))^{-1/2} \qquad (3)$$

ξ_j^s, the sth co-ordinate of the jth 'particle,' and M_j and Q_j its mass (gm.) and charge (E.S.U.) respectively. P_j may be considered another parameter describing another property of the jth particle. It is to be noted that $\varkappa$ is Newton's constant of gravity and that the dimensions of the P_j is that of $(\varkappa)^{-1/2}$ times charge (E.S.U.). M_j, Q_j and P_j could be functions of $X_0(= ct)$ and X_4 satisfying:

$$\partial M_j/\partial t - (13/18\varkappa)^{1/2}c\partial Q_j/\partial X^4 = 0$$
$$\partial Q_j/\partial t - (18\varkappa/13)^{1/2}c\partial P_j/\partial X^4 = 0 \qquad (4)$$

while the partial differential equations of motion for the jth particle in the Newtonian approximation turn out to be:

$$\partial^2\xi_j^s/\partial t^2 - (1/3)(cQ_j/M_j)(26/\varkappa)^{1/2}\partial^2\xi_j^s/\partial X^4\partial t + (P_jc^2/M_j)\partial^2\xi_j^s/\partial X^{42} - \sum_{i\neq j}(\varkappa M_i + Q_iQ_j/M_j - 4\varkappa P_jM_i/(13M_j) + \varkappa P_iP_j/M_j - 4\varkappa P_i/13)\partial V(i,j)/\partial\xi_j^s = 0 \qquad (5)$$

where

$$V(i,j) = ((\xi_i^s - \xi_j^s)(\xi_i^s - \xi_j^s))^{-1/2} \qquad (6)$$

with the time t in seconds units and X^4 the additional co-ordinates expressed in cm. units.

It is to be noted that even for an isolated 'particle' or systems of 'particles' far removed from one another the co-ordinates ξ_j^s satisfy the second-order equation obtained by considering only the first three terms of equation 5 which may be expressed as:

$$(\partial/\partial t - c_{j+}\partial/\partial X^4)(\partial/\partial t - c_{j-}\partial/\partial X^4)\,\xi_j^s = 0 \qquad (7)$$

if M_j, Q_j, and P_j are presumed constant. In equation 7 c_{j+} is given by:

$$c_{j\pm} = (Q_j/M_j)(18\varkappa/13)^{-1/2}\cdot\pm ((Q_j/M_j)^2(18\varkappa/13)^{-1} - P_j/M_j)^{1/2})c \qquad (8)$$

which implies with the f_j^s and g_j^s arbitrary functions of the indicated arguments that:

$$\xi_j^s = f_j^s(c_{j+}t + X^4) + g_j^s(c_{j-}t + X^4) \qquad (9)$$

a wave motion for the ξ_j^s which is propagated with velocities $-c_{j+}$ in our $t - X^4$ space.

The insistence that equation 7 be a hyperbolic partial differential equation has as consequence $P_j/M_j < 0$ to assure this property even when $Q_j = 0$. For an electron the velocity of propagation attains a value of the order 10^{21} times the velocity of light. One would be forced to conclude that if it were possible to communicate in such a space it would be a relatively simple task to assess the state of the far reaches of the universe within a considerably shorter interval of time than heretofore and so indeed to consider occurrences almost anywhere to be of a contemporary nature. In any event the structure of the equations of motion which have emerged even for 'free particles' may perhaps provide us with other conceptual possibilities the starting point of which may lead to a theory with less startling consequences.

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FORTHCOMING EVENTS

Tuesday, January 2

ROYAL GEOGRAPHICAL SOCIETY (joint meeting with the GEOGRAPHICAL ASSOCIATION and the INSTITUTE OF BRITISH GEOGRAPHERS, at 1 Kensington Gore, London, S.W.7), at 3 p.m.—Prof. David Linton: "Some Contrasts in Landscapes in the F.I.D.S. Sector of the Antarctic".

Wednesday, January 3

BRITISH INSTITUTION OF RADIO ENGINEERS (at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1), at 10 a.m.—All-day Symposium on "Data Transmission".

INSTITUTION OF MECHANICAL ENGINEERS, LUBRICATION AND WEAR GROUP (at 1 Birdcage Walk, Westminster, London, S.W.1), at 6 p.m.—Discussion on "Wear of Rubbing Electrical Contacts".

Wednesday, January 3—Friday, January 5

SCIENCE MASTERS' ASSOCIATION (at Imperial College, London, S.W.7), at 10 a.m. daily—Annual Meeting.

Thursday, January 4

INSTITUTE OF REFRIGERATION (at the Institute of Marine Engineers, The Memorial Building, 76 Mark Lane, London, E.C.3), at 5.30 p.m.—Mr. S. I. Neuman: "Refrigeration in Dam Cooling".

INSTITUTION OF ELECTRICAL ENGINEERS (at Savoy Place, London, W.C.2), at 5.30 p.m.—Mr. F. J. Lane: "The Transmission of Power at High Voltages" (Fourth Hunter Memorial Lecture).

ROYAL SOCIETY OF MEDICINE, NEUROLOGY SECTION (at 1 Wimpole Street, London, W.1), at 8 p.m.—Meeting on "Inborn Errors of Metabolism". Speakers: Dr. Richard H. Dobbs, Dr. L. I. Woolf and Dr. G. A. Rose.

Friday, January 5

PLASTICS INSTITUTE (at the Institution of Electrical Engineers, Savoy Place, London, W.C.2), at 2.30 p.m.—Prof. M. Stacey, F.R.S.: "Nature's Plastics" (Annual Young People's Lecture).

SOCIETY OF CHEMICAL INDUSTRY, FINE CHEMICALS GROUP (at 14 Belgrave Square, London, S.W.1), at 6.30 p.m.—Mr. F. P. Doyle: "Recent Advances in the Chemistry of Penicillin".

INSTITUTION OF ELECTRICAL ENGINEERS, MEDICAL ELECTRONICS DISCUSSION GROUP (at Savoy Place, London, W.C.2), at 6 p.m.—Discussion on "Membranes" opened by Dr. H. Davson.

APPOINTMENTS VACANT

APPLICATIONS are invited for the following appointments on or before the dates mentioned:

BIOCHEMIST for the Wellcome Laboratory, situated at the Veterinary Hospital—The Secretary of University Court, The University, Glasgow, W.2 (January 12).

ORNITHOLOGIST (with a good honours degree and/or high professional attainment in ornithology) at London Headquarters, for work on ornithological matters at National level—The Nature Conservancy (E), 19 Belgrave Square, London, S.W.1 (January 12).

LECTURER (with an honours degree or equivalent qualifications, and preferably special interests and experience in general psychology, experimental psychology or statistics) IN THE SCHOOL OF APPLIED PSYCHOLOGY—The Agent-General for New South Wales, 56–57 Strand, London, W.C.2; and the Appointments Section, The University of New South Wales, Box 1, Post Office, Kensington, New South Wales, Australia (January 15).

UNIVERSITY LECTURER (with an honours degree in agriculture, or in agricultural science, together with experience in teaching and research, and preferably with interests in the field of animal husbandry) IN AGRICULTURE—The Secretary of the Appointments Committee of the Faculty of Agriculture, The University, Cambridge (January 16).

RESEARCH FELLOW or RESEARCH ASSISTANT IN PHYSICS at the University of New England, to assist in a programme of research into the physics of ice, water and clouds—The Registrar, University of New England, Armidale, New South Wales, Australia; and The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (Australia and London, January 19).

LECTURER IN GEOGRAPHY—The Registrar and Secretary, The University, 38 North Bailey, Durham (January 20).

LECTURER IN PHYSICS—The Registrar and Secretary, The University, 38 North Bailey, Durham (January 20).

LECTURER (preferably with a major interest in applied mechanics, especially theory of machines, stress analysis and properties of materials, or applied thermodynamics) IN ENGINEERING (Mechanical)—The Registrar, The University, Manchester 13 (January 20).

LECTURERS (2) (suitably qualified honours graduates) IN GEOGRAPHY in the Liberal and Social Studies Department, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana—The Assistant Registrar, Kwame Nkrumah University of Science and Technology, 29 Tavistock Square, London, W.C.1 (January 20).

SCIENTIFIC OFFICER (with a first- or second-class honours degree in mathematics with statistics, or a Diploma in Statistics) IN THE STATISTICS SECTION, for duties mainly concerned with the design and analysis of field and laboratory experiments—The Secretary, The Macaulay Institute for Soil Research, Craigiebuckler, Aberdeen (January 20).

ASSOCIATE PROFESSOR IN CONCRETE TECHNOLOGY at the University of Sydney, Australia—The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (Australia and London, January 24).

LECTURER or ASSISTANT LECTURER IN THE SUB-DEPARTMENT OF COMPUTATION—The Secretary and Registrar, The University, Southampton (January 26).

DEMONSTRATORS (graduates with some research experience) IN THE DEPARTMENT OF ORGANIC CHEMISTRY—The Registrar, The University, Liverpool, quoting Ref. CV/575/N (January 31).

DEMONSTRATORS (2) (with a science degree with a major in zoology) IN ZOOLOGY at the University of Melbourne, Australia—The Registrar, University of Melbourne, Parkville, N.2, Victoria, Australia (January 31).

IMPERIAL CHEMICAL INDUSTRIES RESEARCH FELLOWS (one or more)—The Secretary, The University, Aberdeen (January 31).

LECTURER IN CIVIL ENGINEERING—The Registrar, The University, Sheffield (January 31).

LECTURER IN MECHANICAL ENGINEERING at the University of Hong Kong—The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (Hong Kong and London, January 31).

SENIOR LECTURER IN INORGANIC CHEMISTRY at the University of Natal, Durban—The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (South Africa and London, January 31).

PROFESSOR OF BOTANY; and a PROFESSOR OF ZOOLOGY—The Secretary, University College, Galway, Republic of Ireland (February 5).

IMPERIAL CHEMICAL INDUSTRIES RESEARCH FELLOWS IN THE VARIOUS BRANCHES OF CHEMISTRY, CHEMICAL ENGINEERING, ENGINEERING, TECHNOLOGY, PHYSICS and allied subjects—The Registrar, The University, Manchester 13 (February 14).

TURNER AND NEWALL RESEARCH FELLOWS IN ENGINEERING, INORGANIC CHEMISTRY, PHYSICS and allied subjects—The Registrar, The University, Manchester 13 (February 14).

READER IN MATHEMATICS; and a LECTURER/SENIOR LECTURER IN MATHEMATICS at the University of Western Australia—The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (Australia and London, February 17).

LECTURERS (2) IN FUEL TECHNOLOGY AND CHEMICAL ENGINEERING—The Registrar, The University, Sheffield (February 28).

SENIOR LECTURER IN ELECTRICAL ENGINEERING; and LECTURERS (2) IN ELECTRICAL ENGINEERING at the University of Sydney, Australia—The Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1 (Australia and London, March 1).

LECTURERS, ASSISTANT PROFESSORS or ASSOCIATE PROFESSORS IN THE DEPARTMENT OF MATHEMATICS (either at the Edmonton campus or the Calgary campus)—Prof. M. Wyman, Mathematics Department, University of Alberta, Edmonton, Alberta, Canada.

POSTDOCTORAL ASSISTANT for the operation of a research mass-spectrometer for the detection of unstable reaction intermediates—J. W. Linnett, Inorganic Chemistry Laboratory, The University, Oxford.

RESEARCH ASSISTANT (science graduate), to work with tissue culture in relation to carcinogenesis—Prof. H. N. Green, Department of Experimental Pathology and Cancer Research, School of Medicine, The University, Leeds 2.

SCIENTIFIC OFFICER or SENIOR SCIENTIFIC OFFICER (with an honours degree and experience in microbiology) IN THE BACTERIOLOGY DEPARTMENT, for work on problems involving hygiene and the isolation and classification of micro-organisms—The Secretary, National Institute for Research in Dairying (University of Reading), Shinfield, Reading, quoting Ref. 61/17.

SENIOR HISTOLOGICAL TECHNICIAN TO TAKE CHARGE OF A RESEARCH LABORATORY—Chief Technician, Department of Morbid Anatomy, Institute of Orthopædics, 234 Great Portland Street, London, W.1.

REPORTS and other PUBLICATIONS

(not included in the monthly Books Supplement)

Great Britain and Ireland

Modern Science Memoirs, No. 41: On Teaching Voltaic Cells and Electrolysis. By H. G. Andrews. Pp. 11. (London: John Murray, 1961. Published for the Science Masters' Association.) 2*s.* net. [1710

Department of Scientific and Industrial Research: Forest Products Research. Record No. 31: Non-pressure Methods of Applying Wood Preservatives. By J. Bryan and D. F. Purslow. Pp. iv+14+8 plates. 2*s.* 6*d.* net. Bulletin No. 47: Working Stresses for Structural Timbers. By J. G. Sunley. Pp. iv+18. 1*s.* 3*d.* net. (London: H.M. Stationery Office, 1961.) [1710

Bulletin of the British Museum (Natural History). Geology. Vol. 5, No. 7: The Old Red Sandstone of Brown Clee Hill and the Adjacent Area. 1: Stratigraphy. By Harold William Ball and David Lawrence Dineley. 2: Palaeontology. By Errol Ivor White. Pp. 175–310+plates 33–48. (London: British Museum (Natural History), 1961.) 70*s.* [1710

Building Research Station Digest, No. 15, (Second Series): Pipes and Fittings for Domestic Water Supply. Pp. 5. (London: H.M. Stationery Office, 1961.) 4*d.* [1710

Royal Observatory Bulletins. No. 37: Observations of Southern RR Lyrae Stars. By T. D. Kinman. Pp. 1+E151–204. (London: H.M. Stationery Office, 1961.) 7*s.* 6*d.* net. [1710

British Cast Iron Research Association. Fortieth Annual Report for the year ending 30th June, 1961. Pp. 68. (Alvechurch, Birmingham: British Cast Iron Research Association, 1961.) [1710

London County Council. Public Health Department—Scientific Branch. Annual Report of the Scientific Adviser for the year 1960. Pp. 60 (London: London County Council, 1961.) 1*s.* 3*d.* [1710

University of Oxford: Department of Forestry—Library. List of Periodicals and Serial Publications. Part 1: A–R. Pp. xvii+1–150. Part 2: S–Z. Pp. 151–284. (Oxford: Department of Forestry, The University, 1961.) [1710

Agricultural Research Council: Radiobiological Laboratory. ARCRL No. 5: Surveys of Radioactivity in Human Diet and Experimental Studies, (Report for 1960). Pp. xii+76. (London: H.M. Stationery Office, 1961.) 6s. 6d. [1710

The British National Health Service: a Short Survey with particular reference to the Pharmaceutical Services. Pp. ii+22. (London: The Pharmaceutical Press, 1961.) 5s. [1810

Schools Television: a Discussion Document. Pp. 18. (London: National Union of Teachers, 1961.) 1s. [1810

Imperial College of Science and Technology. Research Report of the City and Guilds College, 1958–1961. Pp. v+96. (London: Imperial College of Science and Technology, City and Guilds College, 1961.) [1810

Advisory Council on Scientific Policy; Committee on Scientific Manpower: Statistics Committee. The Long-Term Demand for Scientific Manpower. Pp. ix+26. (Cmnd. 1490). (London: H.M. Stationery Office, 1961.) 1s. 9d. net. [1810

Royal Institute of Chemistry. Directory of Independent Consultants in Chemistry and Related Subjects. Fourth edition. Pp. iii+34. (London: Royal Institute of Chemistry, 1961.) [1810

Hill Farming Research Organisation. Second Report, 1958–61. Pp. 96. (Edinburgh: Hill Farming Research Organisation, 1961.) [1810

British Drug Houses, Ltd. "Union Carbide" Molecular Sieves for Selective Adsorption. Second edition. Pp. 36. Phosphate Esters in Metabolism: an Account of some Biologically Important Organic Phosphate Compounds. Pp. 39. (Poole: British Drug Houses, Ltd., 1961.) [1810

Ion Exchange Progress, Vol. 1, No. 1, (October, 1961.) Pp. 4. (Lane End, Bucks: Elga Products, Ltd., 1961) [1810

Ministry of Housing and Local Government. Pollution of the Tidal Thames: Report of the Departmental Committee on the Effects of Heated and other Effluents and Discharges on the Condition on the Tidal Reaches of the River Thames. Pp. iv+68+map. (London: H.M. Stationery Office, 1961.) 5s. 6d. net. [1810

Negretti and Zambra, Ltd. Publication No. APP/26: Centralised Temperature Indication for Hotels, Offices, Schools, etc. Pp. 3. Publication No. E/16: Vibration Damping Bracket for use with "Aetec" Instruments. Pp. 2. Publication No. E/19/1: "Aetec" Recording Pyrometers and Resistance Thermometer Recorders. Pp. 8. (London: Negretti and Zambra, Ltd., 1961.) [1810

Annual Report for 1960 (No. 73) of the Marine Biological Station of the University of Liverpool at Port Erin, Isle of Man. Drawn up by J. S. Colman. Pp. 29+1 plate. (Liverpool: The University Press, 1961.) 5s. [2310

Department of Scientific and Industrial Research and Fire Offices' Committee Joint Fire Research Organisation. Fire Note No. 1: Fire-resistance of Floors and Ceilings. By G. I. Bird. Pp. ii+14. (London: H. M. Stationery Office, 1961.) 2s. net. [2310

The Inheritance of Hairy Ear Rims. By R. Ruggles Gates and P. N. Bhaduri. (Mankind Monographs, No. 1) Pp. 38. (Edinburgh: *The Mankind Quarterly*, 1 Darnaway Street, 1961.) 6s.; 1.25 dollars. [2310

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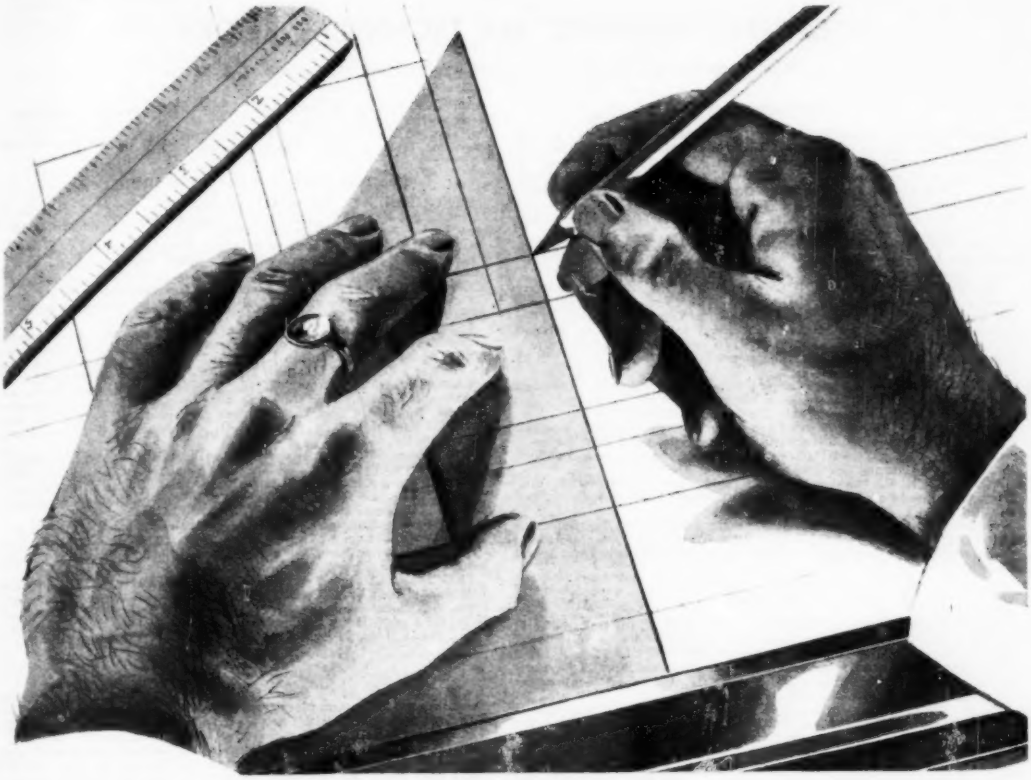

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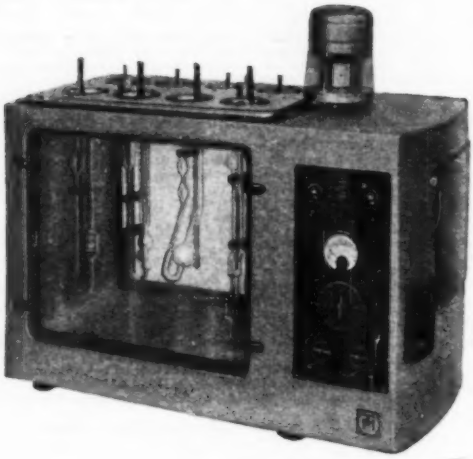

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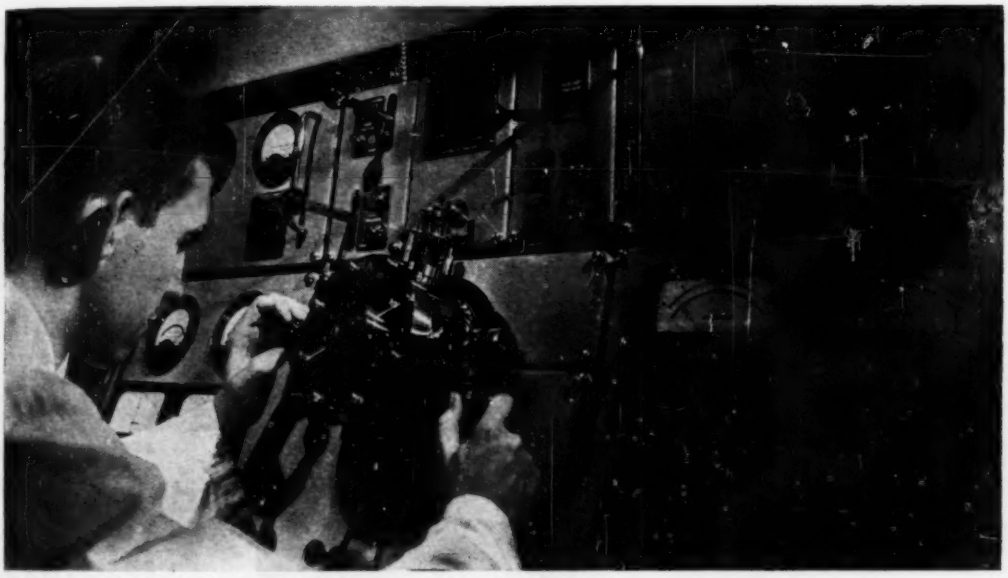

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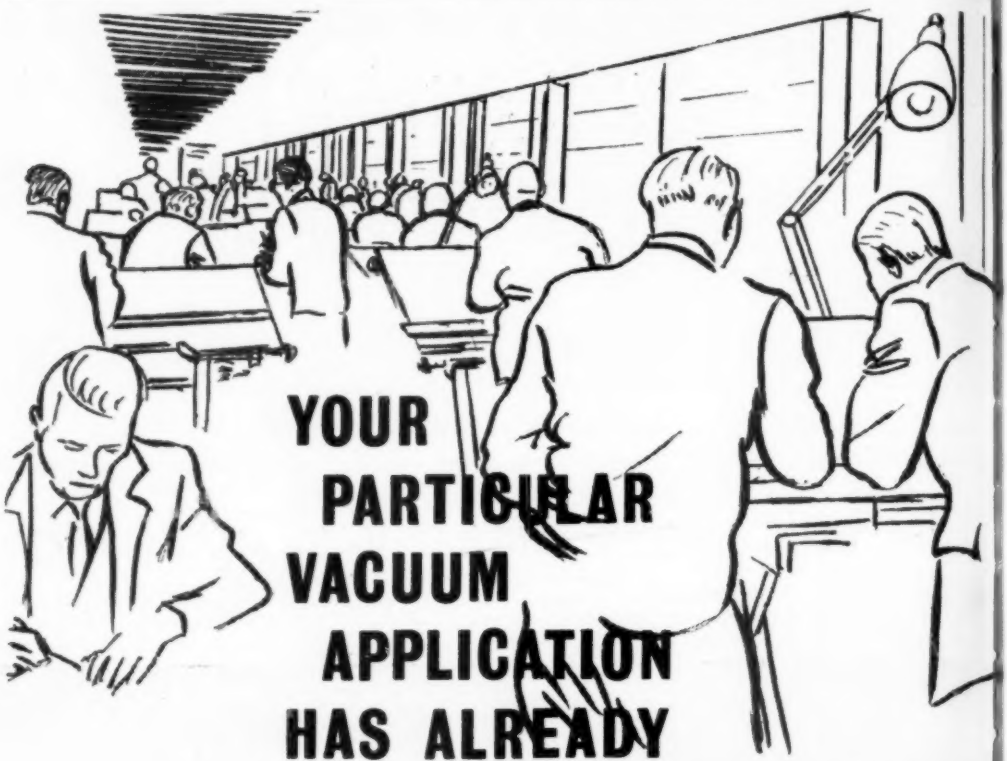

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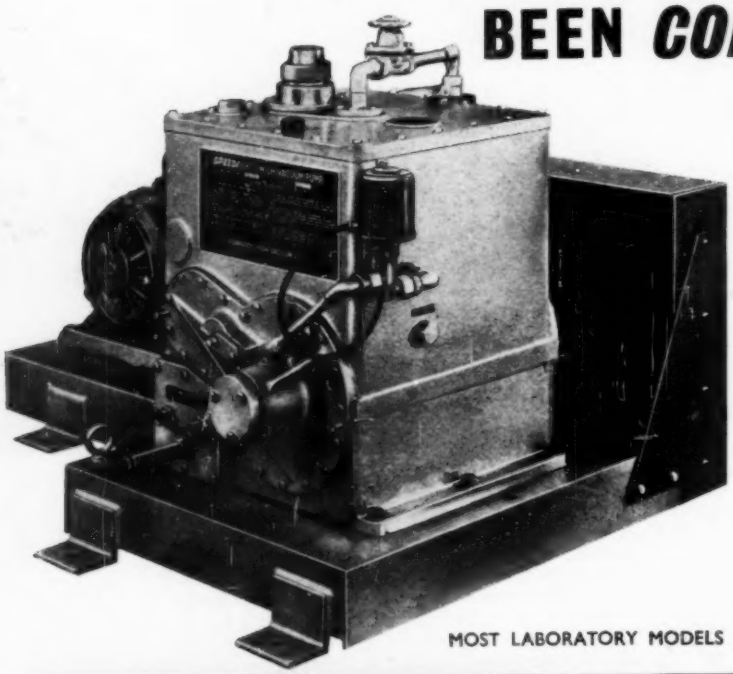

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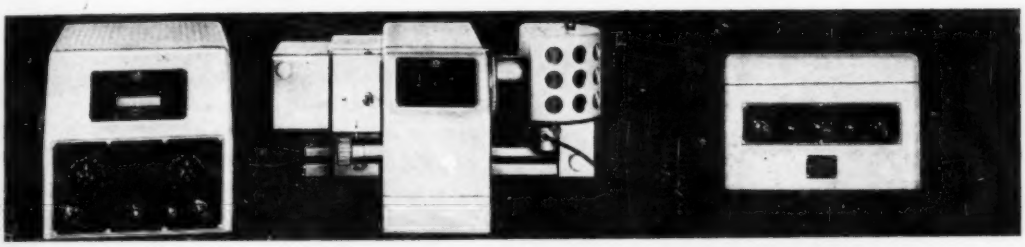

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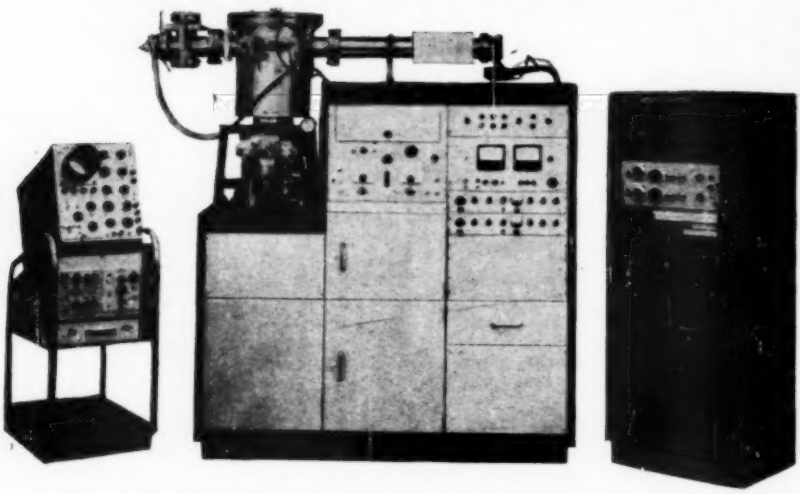

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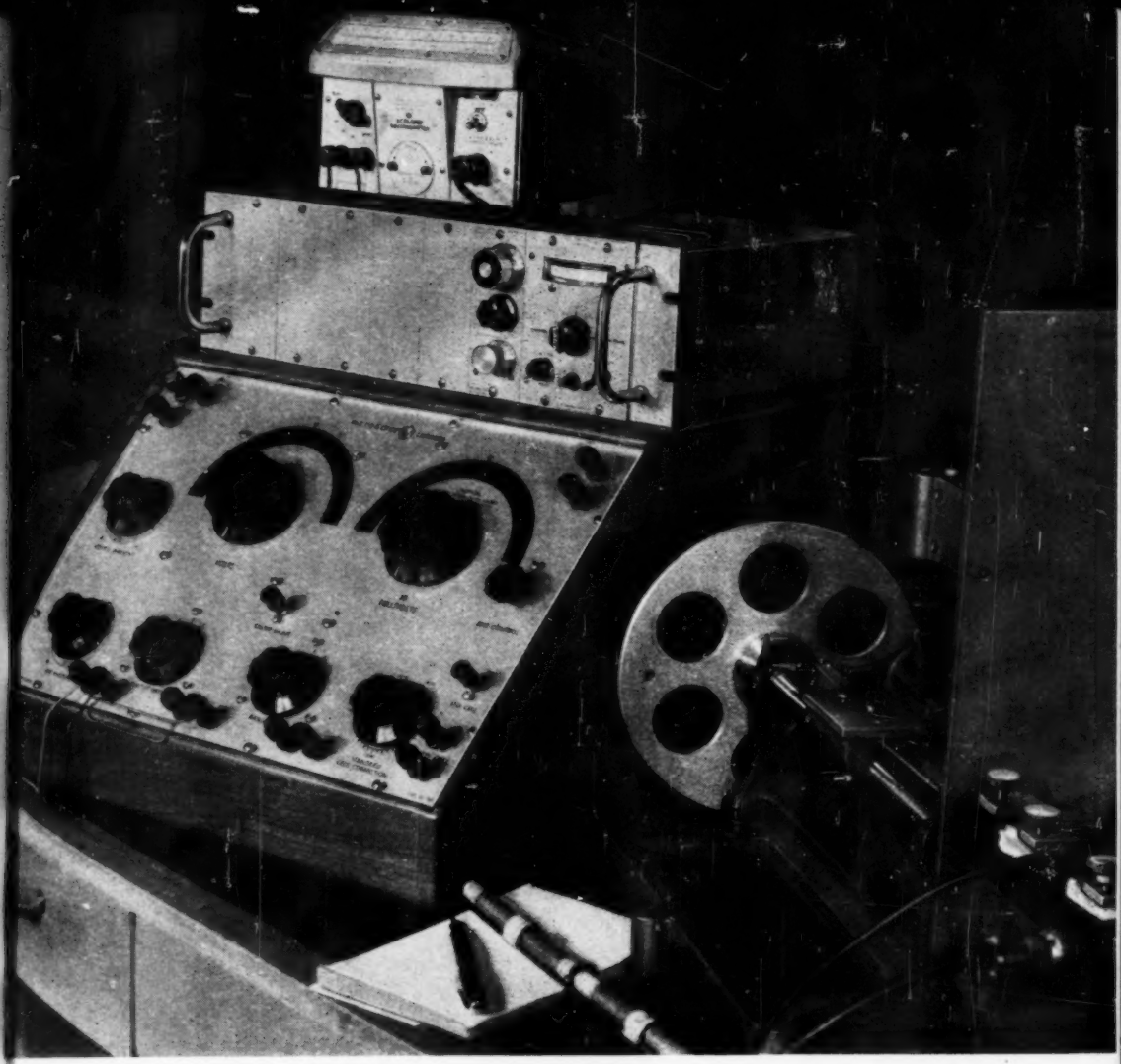

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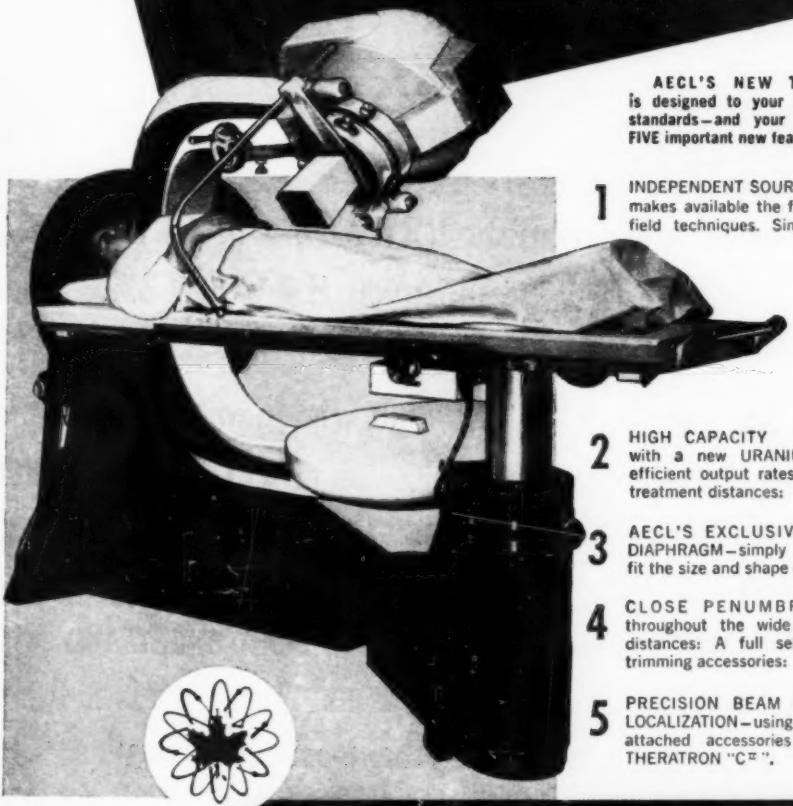

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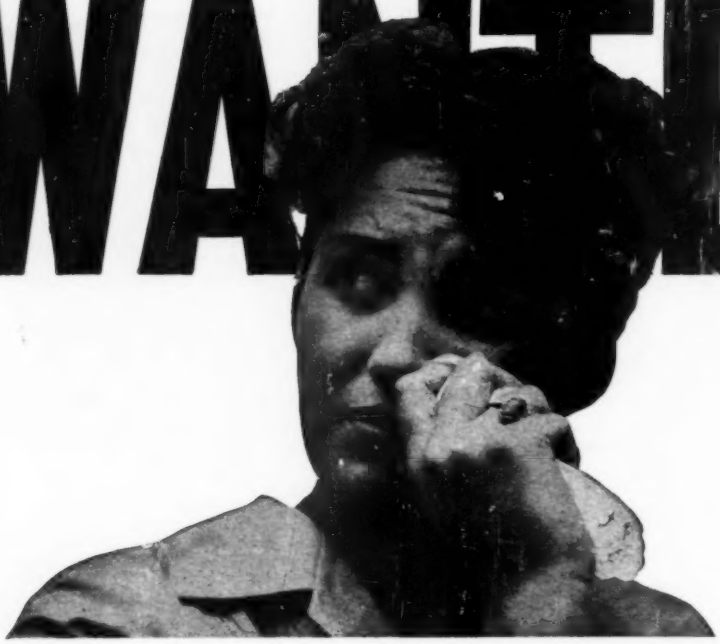

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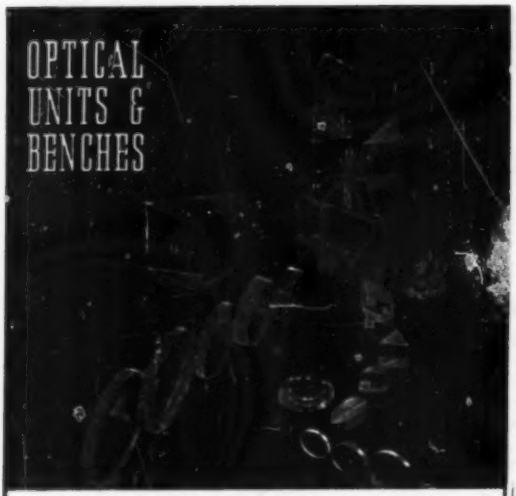

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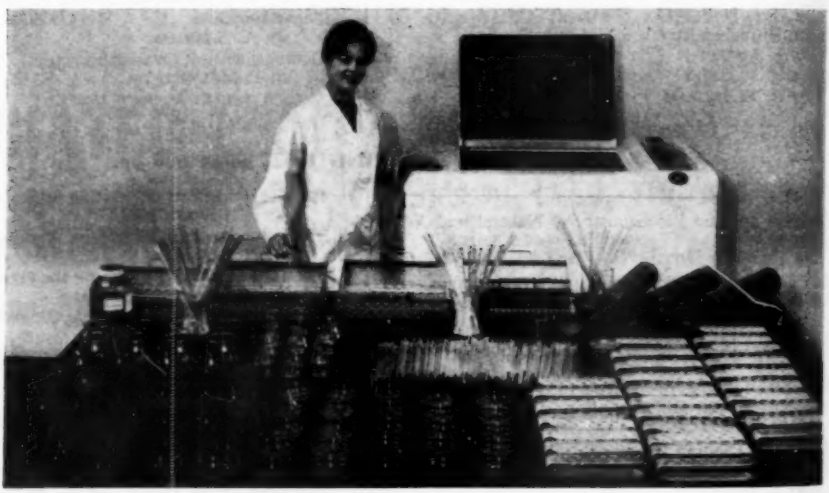

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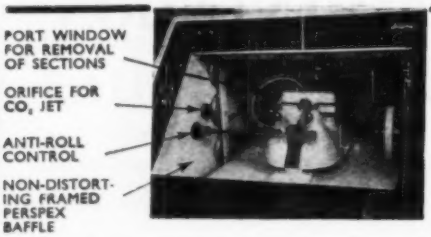

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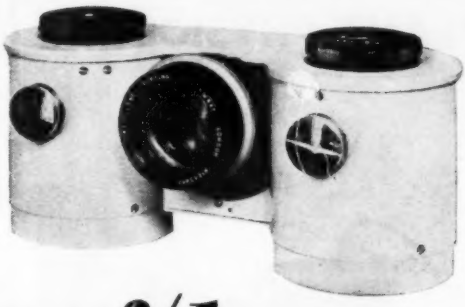

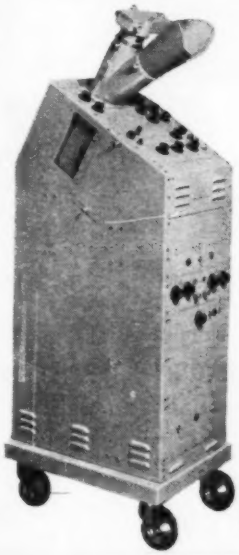

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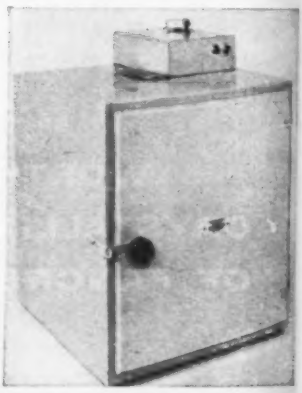

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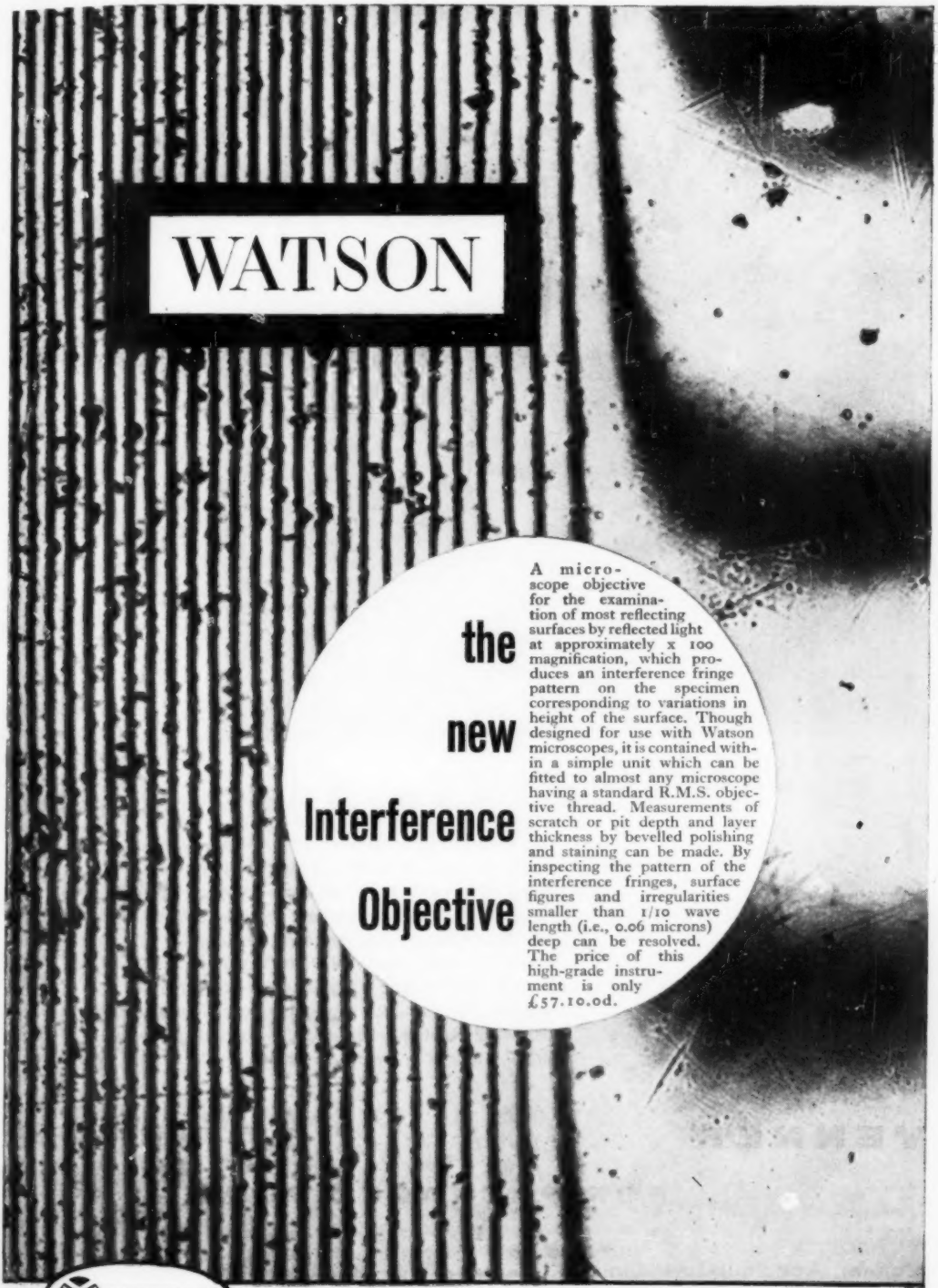
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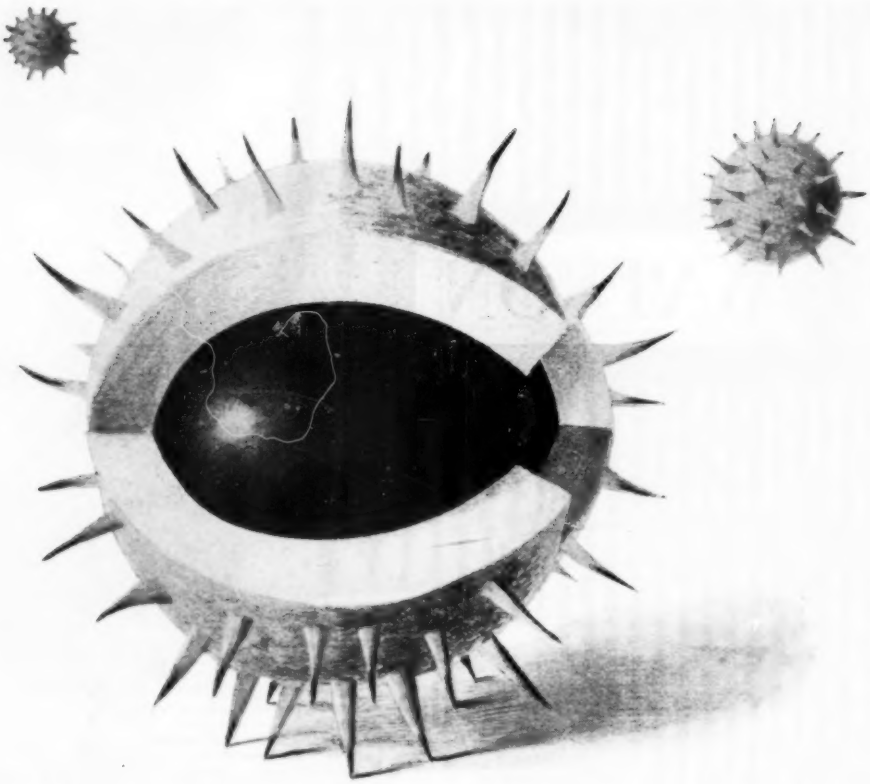

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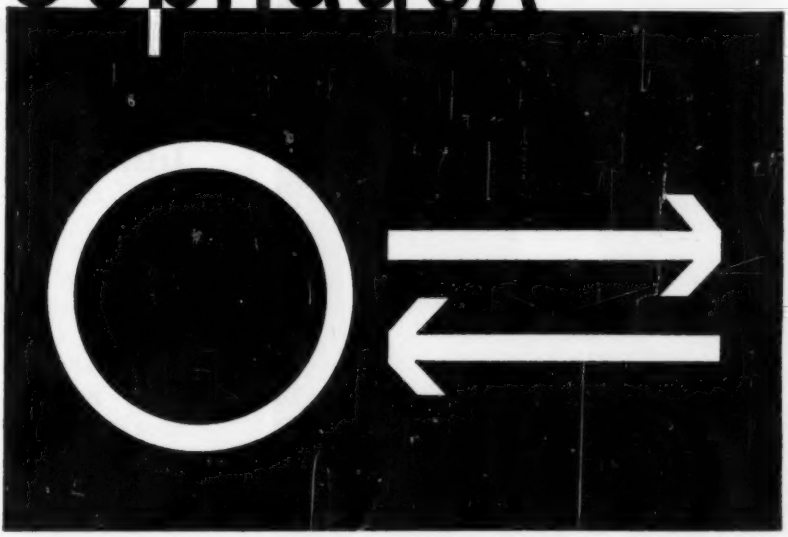

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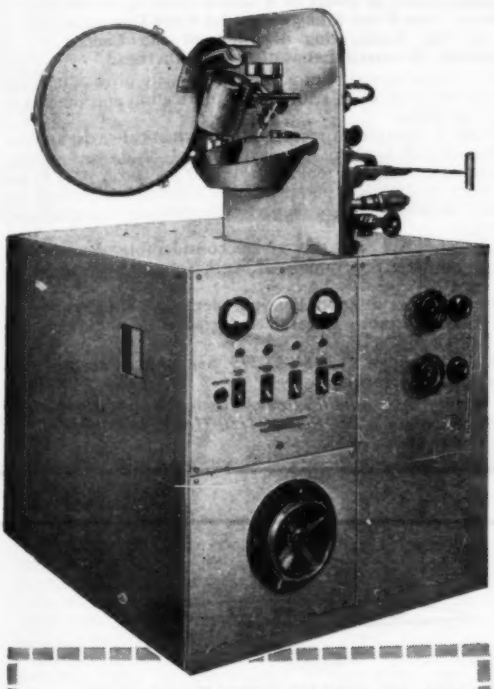

Model 2904

2 lb. to 8 lb. capacity

(FOR OPERATION UP TO 2,000°C)

Made in Britain to the designs of the National Research Corporation of Mass., U.S.A. who have built more high vacuum furnaces now in successful operation than any other firm in the world. The Model 2904 Vacuum Furnace is a self-contained unit for high-temperature operation at high vacuum or under controlled atmosphere. It is heated by a tungsten resistance heating element with molybdenum heat shields in a water-cooled stainless steel sleeve.

This permits:

- Close control of temperature
- Good heat distribution
- Long life
- No outgassing or contamination from refractories

STANDARD EQUIPMENT

- High vacuum pumping system with Wild-Barfield-NRC oil diffusion pump and Gas Ballast mechanical pump.
- Metal cabinet base, overall dimensions 35" x 43" x 34" high.
- Pyrex bell jar, 18" diameter x 12" long, protected with a wire mesh guard, or optionally a stainless steel bell jar.
- Water-cooled basin to shield the bell jar and to catch spilled metal.
- Feed-through for thermocouple wires or heater leads for special work.
- 15 kW. power supply, controlled with a variable auto-transformer. Power is supplied to the split tungsten sleeve through water-cooled coaxial leads.

FOR MELTING • POURING • SINTERING
ALLOYING • HEAT-TREATING • ANNEALING

Vacuum Arc and Vacuum Induction Furnaces
Vacuum Analysis Equipment • Vacuum Diffusion Pumps

* NRC *is the trade-mark of the National Research Corporation, registered in the United States Patent Office.*

WILD BARFIELD **ELECTRIC FURNACES FOR *ALL* HEAT-TREATMENT EQUIPMENT**

WILD-BARFIELD ELECTRIC FURNACES LIMITED

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NRC8

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APPOINTMENTS VACANT

UNIVERSITY OF AUCKLAND
NEW ZEALAND

Applications are invited for the following appointments:

SENIOR LECTURESHIP IN MICROBIOLOGY

For this newly-established post applicants should possess postgraduate qualifications and have had research experience in the organic chemistry and/or biochemistry of nucleic acids. The appointee will be expected to carry out research on nucleic acids in relation to micro-organisms.

LECTURESHIP IN GENETICS

Preference will be given to applicants with training in either (i) microbial genetics (including biochemical genetics); (ii) Drosophila or mouse genetics; (iii) statistical genetics. Applicants should state the particular field in which their research interests lie. It is envisaged that the successful candidate should work not only in the sub-department of genetics but also with the University Department which corresponds with his field of interest, i.e., botany, microbiology, zoology. The person appointed will be expected to engage in active research.

The salary ranges are: Senior Lecturer, £1,750 per annum, rising to £2,000 per annum by three annual increments, two of £100 and one of £50. Lecturer, £1,250 per annum, rising to £1,700 per annum by annual increments of £75 each. Commencing salary within the respective ranges will be determined according to qualifications and experience. Travel and removal expenses are allowed within certain limits.

Further particulars and information as to the method of application may be obtained from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in New Zealand and London, for the Lectureship in Genetics on February 28, 1962, and for the Senior Lectureship in Microbiology on January 26, 1962.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY
(Faculty of Technology in the University of Manchester)

Applications are invited, preferably from organic chemists with Ph.D., for appointment as Research Fellow in the College of Science and Technology (Department of Chemistry) in connection with the development of organic dyes. The investigation is expected to extend over two years under the direction of Dr. A. R. Thompson, Lecturer in Colouring Matters in the University and in the College. Candidates should have research experience in organic chemistry. Stipend £1,000 per annum; F.S.S.U.

Regulations and forms of application may be obtained from the Registrar, The Manchester College of Science and Technology, Manchester 1, to whom applications should be forwarded by January 17, 1962.

IMPERIAL CANCER RESEARCH FUND
RESEARCH ASSISTANT IN DIVISION OF PATHOLOGY

Applications are invited from graduates in medicine or biology interested in cytology, experimental pathology or tissue culture. Some experience desirable but not essential. Appointment initially for three years. Salary in range £850 to £1,250 per annum, depending on qualifications and experience, plus London allowance. Superannuation (F.S.S.U.) and children's allowance.

Three copies of application, with names of three referees, to be sent to the Secretary, Imperial Cancer Research Fund, Lincoln's Inn Fields, London, W.C.2, before January 21, 1962.

Central Electricity Generating Board

GROUP LEADER for FLUID DYNAMICS RESEARCH

Applications are invited from

ENGINEERS and PHYSICISTS

for an appointment as leader of a Group working on the mechanics of Thin Fluid Films within the Fluid Dynamics Section of the Engineering Division at the Central Electricity Research Laboratories, Leatherhead.

The work is of a fundamental nature and is primarily directed towards the solution of problems of shaft sealing and lubrication encountered in advanced generating plant.

At present a team is engaged in research on mechanical seals, and it is intended that this should lead to the development of designs suitable for use in extreme conditions of temperature and pressure, such as are met with in modern boiler feed pumps. It is proposed to extend this work into the field of lubrication, with particular reference to machinery of advanced design.

The successful candidate will be given considerable discretion in formulating an appropriate programme of work for the team under his control.

Candidates must possess a good honours degree in Engineering or Physics and have considerable research experience in an appropriate field.

● ***Salaries within the range £1,715—£2,395 per annum according to qualifications and experience.***

Applications, stating age, qualifications, experience, present position and salary, to the Appointments Officer, 24/30 Holborn, London, E.C.1, by January 15. Quote Ref. N.1553.

CYANAMID

CYANAMID OF GREAT BRITAIN LIMITED
AGRICULTURAL DIVISION

require a

SENIOR LABORATORY TECHNICIAN

to operate a

MOBILE LABORATORY

A mobile field laboratory is to be established to provide laboratory support for certain types of field experiments with new Veterinary and Agricultural Products. Applicants should be Associates or Fellows of the Institute of Medical Laboratory Technology, or possess comparable qualifications. Experience of Veterinary Laboratory diagnostic methods is desirable together with the ability to acquire new techniques in a range of agricultural fields as required. Considerable travel within the United Kingdom will be necessary. The initial salary will be approximately £1,000 per annum, with good employee benefits, including an attractive Pension/Life Assurance scheme.

Suitably-detailed applications, which will be acknowledged, should be addressed, in complete confidence, to:

Personnel Manager
CYANAMID OF GREAT BRITAIN LIMITED
Bush House, Aldwych, London, W.C.2

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You'll find room to expand with
'ENGLISH ELECTRIC' VALVE CO LTD
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Our business is special electronic valves and tubes. Among the many devices we produce will be found:

Image orthicons and vidicons for television cameras, Magnetrons and Klystrons for all types of radar equipment. Storage tubes for "Storing" transient pictures, Semiconductors for power rectifiers. Large and small transmitting valves, travelling wave tubes, parametric amplifiers and other low noise microwave devices.

To support our production and to keep our lead in world markets our research and development teams need men with first-class qualifications and some industrial experience.

We should be pleased to hear from men who think that they have the right background for this work and they should write to: **Group Personnel Services, English Electric House, Strand, London, W.C.2.** Quoting reference number N 1595Q.

'ENGLISH ELECTRIC'

DCL

CHEMICAL RESEARCH

The Chemical Division of The Distillers Company Limited wish to appoint a Section Leader in the divisional Research and Development Department located at their Hull, Yorkshire, factory, where a wide range of organic chemicals are manufactured in bulk. The Department itself comprises modern and well-equipped research laboratories and pilot-plants.

Candidates, preferably aged between 27 and 37, must hold a good honours degree in chemistry. Postgraduate research experience, either academic or in the chemical or allied industries, is essential. The Department undertakes research and development work on new and existing liquid and vapour-phase processes for the manufacture of large tonnage organic chemicals. Each section within the Department is made up of several qualified research chemists; the Section Leader co-ordinates the laboratory work of his section, and collaborates with pilot-plant staff when a project reaches the pilot-plant stage of its development. In the wider sphere, he also contributes to the formulation of the research and development policy of the Department as a whole.

This post demands a real ability and enthusiasm for chemical research, coupled with an originality of mind and versatile approach to the diverse problems that arise; it offers exceptionally challenging prospects for very early promotion, and therefore the man appointed must show not only proven enterprise for the present assignment, but also considerable potential for future progress.

The Company operates a non-contributory pension scheme: assistance can be given to married men towards house purchase and removal expenses.

Write: STAFF MANAGER,
THE DISTILLERS COMPANY LIMITED,
21/22 BOLTON STREET, LONDON, W.1.
Quote Reference: 96/61 N.

UNIVERSITY OF NEW ENGLAND

RESEARCH FELLOW OR RESEARCH ASSISTANT IN PHYSICS

Applications are invited for the position of Research Fellow or Research Assistant to assist in a programme of research into the physics of ice, water and clouds being initiated in the Department of Physics of this University under the direction of Dr. N. H. Fletcher. The appointee will work on experimental problems in solid state physics concerned with the structure and physical properties of ice, silver iodide and related materials. In addition experimental work may be undertaken on some physical properties of clouds in the atmosphere. A Research Fellow should preferably have a doctorate in physics. A Research Assistant would be given the opportunity to work for a higher degree. Previous experience in the particular field of study, while an advantage, is not essential. The commencing salary for the Research Fellow will be determined according to qualifications and experience within the range £A.1,730 by £A.105 to £A.2,435 per annum plus the current cost of living adjustment of £A.47 per annum, and for a Research Assistant within the range £A.845 by £A.65 to £A.1,360 per annum plus the cost of living adjustment. Fares and a removal allowance will be paid for the appointee.

Further information may be obtained from the Acting Registrar, with whom applications (two copies), close on January 19, 1962. Applicants from South Africa and the United Kingdom should forward one copy of their application to the Registrar, University of New England, Armidale, N.S.W., Australia, and an additional copy to the Secretary, Association of Universities of the British Commonwealth, Marlborough House, Pall Mall, London, S.W.1 (from whom additional information may also be obtained) to reach him by the same date.

UNIVERSITY OF MELBOURNE

DEMONSTRATORS (2) IN ZOOLOGY

Applications are invited for the above-mentioned posts. Applicants should have a science degree with a major in zoology. Duties will be mainly demonstrating in second and third year courses in zoology, but some demonstrating in the first year biology course will be expected. The demonstrators will be encouraged to undertake research and may work towards either the M.Sc. or the Ph.D. degree. The Department is well-equipped for research in genetics, cell-physiology, ultrastructure biology, and has recently acquired an extension which includes an aquarium, radioisotope laboratory and specialized facilities for cytogenetics, biochemical genetics and electrophysiology. A high resolution Siemens Electron Microscope is shared with the Botany Department. (A long wheel base Land Rover is used for ecological work.) The Head of the Department is Professor M. J. D. White, F.R.S. Duties begin on March 1, 1962, or as soon as possible thereafter. The salary range is £A.1,120 to £A.1,300 per annum, initial salary depending on qualifications and experience. A grant towards travelling expenses will be made to an appointee from outside Victoria.

Applications should reach the Registrar, University of Melbourne, Parkville, N.2, Victoria, Australia by January 31, 1962.

UNIVERSITY OF SOUTHAMPTON

DEPARTMENT OF MATHEMATICS

Applications are invited for the post of Lecturer or Assistant Lecturer in the Subdepartment of Computation. Salary scales: Lecturer, £1,050 by £50 to £1,400 by £75 to £1,850 with an efficiency bar at £1,475. Assistant Lecturer, £800 by £50 to £950. The initial salary will depend on qualifications and experience.

Further particulars should be obtained from the Secretary and Registrar, The University, Southampton, to whom applications (seven copies from United Kingdom applicants) should be sent not later than January 26, 1962.

PHYSICIST

Victoria College, Victoria, B.C., invites applications for a position to be filled in the Department of Physics from July 1, 1962. Salary and rank will depend upon qualifications and experience. The present salary floors are $9,000 for Associate Professor and $7,000 for Assistant Professor. In addition to teaching, fundamental research is expected. The new science building is now being started and will provide the necessary space and facilities for research.

Inquiries or letters of application should be addressed to the Head of the Department of Physics, Victoria College, Victoria, B.C., Canada.

SCOTTISH & NEWCASTLE BREWERIES LIMITED

CHIEF CHEMIST

NEWCASTLE UPON TYNE

Applications are invited from suitably qualified graduate chemists with experience or interest in Microbiological problems, to take charge of a laboratory devoted to the control and investigation of materials and process of a large progressive brewery, and to participate in developmental and fundamental investigations.

This is a senior position, and will command a suitable salary.

Applications to The Secretary,
THE NEWCASTLE BREWERIES LTD.
Haymarket, NEWCASTLE UPON TYNE, 1

UNIVERSITY OF SYDNEY

SENIOR LECTURESHIP AND LECTURESHIPS IN ELECTRICAL ENGINEERING

Applications are invited for the following positions in the School of Electrical Engineering:

(a) Senior Lectureship in Electrical Engineering. Candidates should be well qualified in Electrical Engineering and have proven research ability. The successful applicant will be required to teach at undergraduate and postgraduate levels and to undertake research. Preference will be given to a candidate who is interested in undertaking research in the field of radio-astronomy.

(b) Lectureships (Two) in Electrical Engineering. Candidates should be well qualified in Electrical Engineering or Physics and able to undertake teaching and research in one or more of the fields of power engineering, electronics, solid state circuits and devices, circuit theory, control systems, computers or energy conversion.

The salary for a Senior Lecturer is within the range £A.2,550 by £A.95 to £A.3,000 per annum; for a Lecturer within the range £A.1,730 by £A.105 to £A.2,435 per annum. In each case cost of living adjustments (at present £A.47 per annum) will be allowed. The salary is subject to deductions under the State Superannuation Act. The commencing salary will be fixed according to the qualifications and experience of the successful applicants.

Further particulars and information as to the method of application may be obtained from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Mariborough House, Pall Mall, London, S.W.1. Applications close in Australia and London on March 1, 1962.

UNIVERSITY OF HONG KONG

LECTURESHIP IN MECHANICAL ENGINEERING

Applications are invited for the abovementioned post. Applicants must be graduates of a British Commonwealth University or of equivalent status, and should preferably be Corporate Members of the Institution of Mechanical Engineers. The successful candidate will be required to teach engineering subjects, including fluid mechanics, to degree level, and to supervise research in this field. Annual salary (superannuable) is £2,150 by £75 to £2,825 (man) or £1,600 by £60 to £2,140 (woman). The equivalent of income tax in the Colony is comparatively low. Air passages (or first class sea passages of equivalent cost to tourist air passages) are provided for expatriate staff on first appointment and leaves. Accommodation at reasonable rental is provided for those recruited from abroad.

Further particulars and information as to the method of application may be obtained from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Mariborough House, Pall Mall, London, S.W.1. Applications close, in Hong Kong and London, on January 31, 1962.

RADIOCHEMIST

The National Physical Laboratory, Teddington, requires a radiochemist in the Senior Scientific Officer/Scientific Officer grades to investigate some or all of the following problems: (1) The production of thin uniform, quantitative sources for $4\pi\beta$ counting. (2) The adsorption of radioactivity on glass and polythene. (3) Separation and purification of radionuclides. (4) Chemical dosimetry. In addition there will be opportunities for investigations using a 3 MeV Van de Graaff neutron generator. This post offers a unique opportunity for the right person in an expanding section of the Laboratory. Adequate experimental facilities and supporting staff will be provided. The officer should have drive and initiative and be of such academic standing that he can work largely on his own. Qualifications: First- or second-class honours degree in chemistry or equivalent. For the senior post at least three years' postgraduate research experience is required. Salaries: Scientific Officer, £773 to £1,267; Senior Scientific Officer, £1,392 to £1,714. Forms from Director, address above quoting 65 ZY. Closing date January 20, 1962.

CHLORIDE ELECTRICAL STORAGE COMPANY LTD.

has a vacancy for a

LIBRARIAN
(Female)

to work in a special library serving their Group of Companies.

Her duties will include compilation of bibliographies, classification, and the editing of translations. Special emphasis will be placed on her ability to compile indices and to abstract intelligently.

The successful applicant must have completed part of her training towards the A.L.A. qualifications.

Salary according to age and experience. Hours of work 9 a.m. to 5 p.m. Five-day week. Excellent canteen facilities.

Applications should be sent to the Chief Personnel Officer, Exide Works, Clifton Junction, Manchester.

ROYAL COLLEGE OF SURGEONS

DEPARTMENT OF PHARMACOLOGY EXAMINATION HALL, QUEEN SQUARE, LONDON, W.C.1

Head Technician wanted with considerable experience in administration, general laboratory techniques, and workshop practice. Salary: Whitley Scales in Senior Technician grades. Applications by January 15, 1962.

B.B.C. REQUIRES EDITOR, NATURAL History Unit in Bristol. The B.B.C. Natural History Unit, with its own complement of Producers and Film Research and Library Staff, provides programmes for the B.B.C.'s national service in Television and Sound. The Editor is responsible, under general direction of Head of Programmes, West Region (where the Unit is based) for professional standards of the output and organization of the staff. In addition to his own production work he will maintain liaison with outside bodies, particularly in scientific and academic fields, and should stimulate creative expression in terms of broadcasting. The post requires appropriate specialist qualifications as a naturalist and professional experience in at least one relevant sphere of production (television, film or sound broadcasting). Some practice in administration and financial negotiation desirable. Salary £2,425 rising by five annual increments to £3,025 maximum per annum. Appointment might be made initially at a lower grade where an otherwise well qualified candidate required some technical training in production, or where an expert broadcasting practitioner needed time and opportunity to become more closely acquainted with the Unit's specialized activities.—Requests for application forms (enclosing addressed envelope and quoting reference 61.G.575 N), should reach Appointments Officer, Broadcasting House, London, W.1, within five days.

TWO-PHASE FLOW

A graduate Engineer or Physicist is required to be responsible for long term fundamental research work on thermodynamic, heat and mass transfer and fluid flow problems associated with two phase (liquid/gas) flow processes. Circuit studies include the investigation of wet steam flow and condensation.

Experience in this field is not essential but some research experience would be an asset.

Salary £900 to £1,300 per annum.

Please reply to Box No. 603, T. G. Scott and Son, Ltd., 1 Clement's Inn, London, W.C.2.

ASSUMPTION UNIVERSITY OF WINDSOR

DEPARTMENT OF PHYSICS WINDSOR, ONTARIO, CANADA

Graduate Assistantships. The Department of Physics offers teaching and research assistantships to students qualified for admission to graduate studies. Fields of research include beta- and gamma-ray spectroscopy, electron spin resonance, optical pumping, atomic collisions and lifetime measurements of excited states in atoms. Stipends up to $2,800 per annum, depending on qualifications and duties in the department.

Postdoctorate Fellowships. Applications are invited from candidates wishing to engage in experimental research either in the field of optical pumping or in problems of energy transfer in atomic collisions. The stipends amount to $5,000 for unmarried Fellows or $5,000 for male married Fellows.

Inquiries concerning both Graduate Assistantships and Postdoctorate Fellowships should be addressed to Dr. L. Krause, Chairman, Department of Physics, Assumption University of Windsor.

AUSTRALIA

THE UNIVERSITY OF NEW SOUTH WALES LECTURER APPLIED PSYCHOLOGY

The University of New South Wales wishes to appoint a Lecturer to the staff of the School of Applied Psychology. Applicants should have a good honours degree or equivalent qualification. Special interests and experience in general psychology, experimental psychology or statistics would be particularly valuable. Salary: £A.1,777 rising to £A.2,482 per annum. Commencing salary will be determined by qualifications and experience. Successful applicant will be eligible subject to medical examination to join the State superannuation scheme. Other staff benefits include study leave and assistance with housing. First-class ship fare to Sydney for appointee and family will be paid.

Four copies of applications, including the names of two referees, should be lodged with the Agent General for New South Wales, 56-57 Strand, London, W.C.2, and a copy forwarded to the Appointments Section, The University of New South Wales, Box 1, Post Office, Kensington, N.S.W., by airmail to reach there before January 15, 1962.

SCOTTISH MARINE BIOLOGICAL ASSOCIATION

OCEANOGRAPHIC LABORATORY EDINBURGH

Assistant Experimental Officer required for the analysis of plankton samples in the Continuous Plankton Recorder Survey of the North Atlantic Ocean and the North Sea. Minimum qualification: G.C.E., Scottish Leaving Certificate or equivalent, with passes in specified subjects at Advanced or Higher levels but preference will be given to graduates in botany or zoology. Salary according to age, £458 (age 18) to £801 (age 25) and, by annual increments, to £983; thereafter depending on promotion. Contributory Superannuation Scheme.

Requests for further particulars and application forms should be made as soon as possible to the Officer-in-Charge, Oceanographic Laboratory, 78 Craighall Road, Edinburgh, 6. Non-graduates should include a statement of the passes in the qualifying examination.

PRINCE OF WALES HOSPITAL
AVOCA ST. RANDWICK, N.S.W., AUSTRALIA

UNIVERSITY OF NEW SOUTH WALES MEDICAL BIOCHEMIST

Applications are invited for appointment as Medical Biochemist at the Prince of Wales Hospital, which is a teaching hospital in the new medical school of the University of New South Wales.

Salary scale: Medical Graduates £3,204 to £4,164; Science Graduates, £2,311 to £2,787, the initial salary depending on qualifications and experience. The successful candidate will be eligible for conjoint university appointment at the level of Senior Lecturer or Associate Professor, such appointment carrying an additional remuneration of £500 or £750 respectively.

First class fares to Sydney will be paid for the appointee and his family, and the successful candidate will be eligible, subject to satisfactory medical examination, to contribute to superannuation after twelve months service.

With the approval of the University and its bankers, married men may be assisted by loans with the purchase of a house.

The appointee will be expected to develop the hospital's facilities for biochemistry, including the planning of laboratories in a proposed building programme, to establish research work and to collaborate in teaching medical biochemistry in the medical school.

Applications should be sent with names of three referees to the undersigned, from whom further information may be obtained. Closing date January 30, 1962.

R. F. KAYE-WEBSTER,
Medical Superintendent and
Chief Executive Officer.

McMASTER UNIVERSITY
POST-DOCTORAL FELLOWSHIPS IN PHYSICS

Applications are invited for National Research Council and other Post-doctoral Fellowships, tenable in the Department of Physics, McMaster University. Successful applicants may choose to work full-time on their research or to supplement their research with a modest amount of lecturing.

Inquiries and applications should be addressed to Professor M. W. Johns, Chairman, Department of Physics, McMaster University, Hamilton, Ontario, Canada.

ASSISTANT AGRICULTURAL ADVISER
ADEN

To take responsibility for agriculture in a large area and arrange and supervise experimental work. Duties require a knowledge of cultivation under flood and well irrigation and include some administrative work for the running of a protectorate station. Candidates (male), between 25-35, must have a degree in agriculture or equivalent with experience in arid zone agriculture and a knowledge of spoken Arabic. Appointment on short term contract, with a gratuity of 12½ per cent of aggregate salary, for one tour of 18-24 months, or, on probation for the permanent establishment. Salary in range £1,281 to £2,409. Free passages. Generous leave. Furnished accommodation, normally available, at low rental. Children's education allowances.

Apply, stating full name and giving brief details of qualifications and experience, to Director of Recruitment, Department of Technical Co-operation, Carlton House Terrace, London, S.W.1. Quote C1/RC 213/1/02.

POSITION AVAILABLE

An addition to the staff of the Geology Department at Mount Allison University has been authorized. The Department therefore invites applications from those interested in teaching palaeontology and stratigraphy and developing research in these fields. Applicants should have a Ph.D. or equivalent and a desire to pursue research work in the above fields. Preference will be given to those with field and/or research experience as well as teaching ability. The position is tenable from July 1, 1962, and whilst the initial appointment is probationary for one year, a permanent position exists. The college year leaves at least four months free during the summer for field or laboratory work.

Applications, giving age and other personal information, particulars of academic and other qualifications and experience, names and addresses of references concerning the applicant's suitability for the position, should be addressed to the Head, Department of Geology, Mount Allison University, Sackville, New Brunswick, Canada.

A.G.I. LTD.
RESEARCH AND DEVELOPMENT ORGANIZATION
105/107 LANSDOWNE ROAD, CROYDON

Require **male or female Laboratory Assistant** for the Physics Department.

Applicants should have G.C.E. "A" Level in Physics and Mathematics and/or be studying for B.Sc. or membership of a senior Institution.

Please write or phone CROydon 8282 in the first instance for an interview appointment.

INSPECTOR OF MINES
NORTHERN RHODESIA

Qualifications: Diploma or degree in mining of recognized School of Mines or University, with at least five years experience, preferably in metalliferous mining industry, including knowledge of underground ventilation practice.

Age limits: 25-45.

Duties: Enforcement of mining and explosives legislation, inspection of mines and accident investigation.

Terms of appointment: On contract for a tour of 36 months in the first instance.

Emoluments in the scale £1,065 to £2,245 plus gratuity of £37 10s. for each three months' satisfactory service. Free passages. Quarters at rental. Free medical attention. Generous leave. Taxation at local rates. Apply to Director of Recruitment, Department of Technical Co-operation, Carlton House Terrace, London, S.W.1, stating full name, age, qualifications and experience and quoting RC 242/108/01/C1.

UNIVERSITY OF AUCKLAND
NEW ZEALAND
LECTURESHIP IN PSYCHOLOGY

Applications are invited for the above-mentioned post. Applicants should possess post-graduate qualifications and have research interests in experimental or social psychology. The salary scale for the position is £1,250 per annum rising to £1,700 per annum by annual increments of £75. Commencing salary within this scale will be determined according to qualifications and experience.

Further particulars and information as to the method of application may be obtained from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in New Zealand and London on February 15, 1962.

CITY OF LEICESTER EDUCATION COMMITTEE
LEICESTER COLLEGE OF TECHNOLOGY AND COMMERCE
Principal: R. E. Wood, M.Sc., F.Inst.P.

Applications are invited for the post of Senior Lecturer in Pharmacology in the Department of Biology. Applicants should possess a good honours degree and should be able to teach the subject for courses leading to the University of London External B.Pharm. degree. Opportunity will be given for research. Salary: Burnham Technical Scale, £1,800 to £2,000 per annum.

Application forms and further particulars may be obtained from the Registrar, Leicester College of Technology and Commerce.

MEDICALLY QUALIFIED RESEARCH Worker with experience in tissue culture is required by the Medical Research Council Human Bio-Chemical Genetics Research Unit. Salary within the range £1,250 to £1,975 (plus London allowance and child allowances), according to qualifications and experience.—Applications to Professor H. Harris, Department of Bio-Chemistry, King's College, Strand, London, W.C.2.

UNIVERSITY OF EDINBURGH

Applications are invited for I.C.I. Research Fellowships in Biochemistry, Chemistry, Engineering, Pharmacology, Physics or Chemical Technology (Chemical Engineering) normally tenable for a period of three years. Applicants should preferably hold the degree of Ph.D., or have equivalent research experience. Appointments will date from October 1, 1962 (or earlier in the case of selected candidates who may be available before that date). The initial salary will depend upon qualifications and experience, but will normally be within the range £800 to £1,100 per annum, together with F.S.S.U. benefits and family allowance. In the case of an overseas applicant, the University is also prepared to consider the provision of an allowance towards defraying the cost of travel to and from Great Britain. Forms of application and further particulars may be obtained from the undersigned.

Applications (two copies), should be submitted not later than February 16, 1962.

CHARLES H. STEWART,
Secretary to the University.

ST. VINCENT'S SCHOOL OF MEDICAL RESEARCH
MELBOURNE, AUSTRALIA

Applications are invited for the post of Senior Research Assistant in Biochemistry. The appointee will be engaged full time in a research programme in the field of protein chemistry. Applicants should possess a higher degree in Chemistry or Biochemistry, and should have several years experience in biochemical research. The salary range is £A.2,250 to £A.2,750 per annum. Superannuation will be available under the Institutional Staff Superannuation Fund Scheme. Travel expenses for appointee and his family from the home country to Australia and back will be paid for service of at least three years and pro rata for a shorter period.

Applications, stating full name, age, marital status, particulars of qualifications and experience, and the time when the applicant would be free to assume duty and accompanied by copies of testimonials, should be sent to the Director of Research, Dr. Pehr Edman, St. Vincent's School of Medical Research, Victoria Parade, Fitzroy N.6, Victoria. The closing date for applications is February 28, 1962.

UNIVERSITY COLLEGE OF NORTH WALES
BANGOR

Applications are invited for the post of Lecturer or Assistant Lecturer in the Department of Zoology. Candidates should have qualifications in genetics or cytogenetics. The salary scale for a Lecturer is £1,050 by £50 to £1,400 by £75 to £1,850, and for an Assistant Lecturer £800 by £50 to £950. In addition there are F.S.S.U. benefits and family allowances. The appointment will date from October 1, 1962.

Two copies of the application should reach the Registrar, from whom further particulars may be obtained, not later than January 18, 1962.

UNIVERSITY OF LONDON
THE MEDICAL COLLEGE OF ST. BARTHOLOMEW'S HOSPITAL
WEST SMITHFIELD, E.C.1

Chief Technician required in the Physics Department to help in research work and in the general running of the department. The main lines of research are effects of radiations, using a 15 MeV. linear accelerator, medical uses of radioactive isotopes and nuclear physics. Considerable experience in electronics, vacuum technology, scientific instrumentation and general laboratory techniques required. Salary according to Whitley Council scale.

Applications, with the names of three referees, to be submitted to the Secretary of the Medical College, not later than January 15, 1962.

UNIVERSITY OF SOUTHAMPTON

Applications are invited for the post of Lecturer or Assistant Lecturer in Pure Mathematics. Salary scales: Lecturer, £1,050 by £50 to £1,400 by £75 to £1,850 with an efficiency bar at £1,475. Assistant Lecturer, £800 by £50 to £950. The initial salary will depend on qualifications and experience.

Further particulars should be obtained from the Secretary and Registrar, The University, Southampton, to whom applications (seven copies from United Kingdom applicants), should be sent not later than January 26, 1962.

XUM

UNIVERSITY OF WESTERN AUSTRALIA

READERSHIP IN PHYSICS

Applications are invited for appointment to the above-named position in the Department of Physics. Preference will be given to persons having research experience in low temperature physics. A Collins Helium Liquefier will be installed in the new physics building now under construction and due for completion early in 1962. The University has also ordered an I.B.M. 1620 Computer which will be installed in the Department of Physics in August, 1962. The salary range for the position is at present £A.3,010 by £A.60 to £A.3,250 per annum, but it is expected that this range will be increased in the near future to £A.3,000 by £A.100 to £A.3,300 per annum. Superannuation will be similar to F.S.S.U.

It is important that intending applicants obtain details of the procedure to be followed in applying for the position and a copy of the conditions of appointment before submitting their applications. This information is available from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in Australia and London on January 31, 1962.

UNIVERSITY OF NATAL

DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY

Applications are invited from suitably qualified persons for appointment to the post of: Senior Lecturer in Inorganic Chemistry, Durban. The salary scale attached to the post is R.3,180 by R.120 to R.4,140 (£1,590 by £60 to £2,070) per annum. The commencing notch on the above salary scales will be dependent on the qualifications and/or experience of the successful candidate.

Application forms and further particulars of the post are obtainable from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in South Africa and London on January 31, 1962.

UNIVERSITY OF OTAGO

DUNEDIN, NEW ZEALAND

SENIOR LECTURER IN PHYSIOLOGY

The Council of the University of Otago, Dunedin, New Zealand, hopes shortly to appoint a Senior Lecturer in the Department of Physiology of the Medical School. Applicants should be medically qualified and have had a number of years' experience of teaching and of postgraduate research in physiology. The salary of a medical graduate employed as a senior lecturer in the preclinical Departments of the school is in the range £2,075 to £2,525.

Further information may be obtained from the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in New Zealand and London on February 28, 1962.

RESEARCH DEVELOPMENT CHEMIST REquired with experience of pilot scale fine chemical drug manufacture. This is a senior post and offers an excellent opportunity for experienced well qualified organic chemist with good academic background.—Write in first instance, giving full particulars, to: The Managing Director, Biorex Laboratories Ltd., 47/51 Exmouth Street, London, E.C.1.

INSTRUMENT-MAKER REQUIRED FOR work on prototype Medical Research Apparatus. O.N.C. (or equivalent) in Instrument Making preferred. Age: 21-27 years. Salary according to age and experience. Five-day week.—Apply, with details of education and experience to: The Director, Toxicology Research Unit, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

SENIOR ELECTRONIC TECHNICIAN, AGE 21 to 30, required for new Medical Engineering Laboratories to develop, construct and maintain electronic and other types of equipment for use in medical research. Applicants with previous experience in this field and holding an H.N.C. or O.N.C. will be given preference. Salary scale £625 to £1,000 per annum, but applicants with higher qualifications may be appointed technical officer in the range £700 to £1,250 per annum.—Application forms from Secretary, Postgraduate Medical School, Ducane Road, W.12.

CONNAUGHT HOSPITAL

WALTHAMSTOW, E.17

Senior Laboratory Technician I required in the Bacteriology Department of the above hospital. Excellent opportunities for study for the Final Bacteriology examination.

Forms of application may be obtained from Secretary, Forest Group H.M.C., Langthorne Road, Leytonstone, E.11.

BRITISH GUIANA

SENIOR GEOLOGIST AND GEOLOGIST

(1) SENIOR GEOLOGIST. Qualifications: First- or upper second-class honours degree in geology with at least three years experience. Research experience, ability to supervise the work of others, and special knowledge of, and experience in, igneous and/or metamorphic rocks, structural geology and prospecting as well as training in economic geology are desirable.

Duties: To organize a team of geologists engaged in geological mapping and prospecting and the investigation of mineral deposits.

(2) GEOLOGIST. Qualifications: First- or upper second-class honours degree in geology or mining geology. Experience desirable.

Duties: General geological mapping and mineral investigation in the interior. Work mainly on precambrian crystalline rocks with emphasis on petrographical, structural and economic studies.

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Apply to Director of Recruitment, Department of Technical Co-operation, Carlton House Terrace, London, S.W.1, quoting RC 218/16/03/C1 for Senior Geologist and RC 218/16/01/C1 for Geologist vacancy and giving full name, age, qualifications and experience.

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Required for an engineering company situated in the Slough area. Applicants (male or female) should be over 24 years of age and have experience of special library work including U.D.C. classification. Consideration would also be given to applicants with library experience outside the engineering industry. Attractive salary and immediate entry into the Company's superannuation and life assurance scheme. Please reply, giving full details and quoting ref. 7176, to

Box 604, T. G. Scott and Son, Ltd., 1 Clement's Inn, London, W.C.2.

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1. Applications are invited for the following posts in the Department of Botany, duties to commence October 1, 1962. (1) Lecturer in Microbiology; salary scale £1,050 to £1,850 plus £60 London allowance. Interest in bacteria or viruses. (2) Assistant Lecturer in Botany; salary scale £800 to £950 plus £60 London allowances. F.S.S.U. and family allowance for both posts.—Applications should be sent by January 22, 1962, to the Secretary, from whom further particulars may be obtained.

UNIVERSITY OF ST. ANDREWS

Applications are invited for a Senior Lecturership or Lectureship in Electronic Physics, in the Department of Electrical Engineering, Queen's College, Dundee, to commence on a date to be arranged. Candidates should preferably possess a Ph.D. degree in physics and suitable experience in electronics. Salary scales: Senior Lecturership £1,925 by £75 to £2,425; Lectureship, £1,400 by £50 to £1,400 by £75 to £1,850 (efficiency bar £1,400). F.S.S.U.; family allowance and grant towards furniture removal expenses.

Applications (six copies), containing the names of three referees, to be lodged with the Secretary of the University, Queen's College, Dundee, from whom further particulars may be obtained, not later than January 20, 1962.

INORGANIC CHEMIST: Ph.D.

Applications are invited for a staff appointment starting in July, 1962. Preference will be given to a specialist in X-ray crystallography and structure analysis. Salary and rank will be commensurate with qualifications and experience.

Please send inquiries and a résumé of background to Professor F. L. M. Pattison, Head, Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

UNIVERSITY OF OXFORD

Post-doctoral Assistantship for operation of research mass-spectrometer for detection of unstable reaction intermediates. Salary £800 to £1,000 per annum; to start on October 1, 1962, for one or three years.

Further details from J. W. Linnett, Inorganic Chemistry Laboratory, Oxford.

GRADUATE CHEMIST OR BIOCHEMIST required for Research and Development Laboratories of well-known Company in City of London. Previous experience in the isolation of biochemical materials from natural sources is essential. Non-contributory Pension Scheme.—Write, giving age and details of experience and qualifications to Box 602, T. G. Scott and Son, Ltd., 1 Clement's Inn, London, W.C.2.

RESEARCH ASSOCIATE OR ASSISTANT Ph.D. or Ph.D. candidate interested in defect crystalline structure as applied to mechanical properties of materials. Start Spring of 1962. Write to Dr. J. Marin, Department of Engineering Mechanics, The Pennsylvania State University, University Park, Pennsylvania, U.S.A.

THE EVANS MEDICAL RESEARCH Laboratories require a Head of the Pharmaceutical Department responsible for formulation and development (on appointment of the present holder to an academic post). Modern laboratories offering good scope in an expanding British organisation.—Applications to the Director of Research, Evans Medical Ltd., Liverpool 24.

THE ROYAL SOCIETY INTENDS TO MAKE a senior appointment to its administrative staff and invites applications. Applicants should preferably be between 40-45 years of age, having high scientific qualifications including considerable research experience and some familiarity with administration of scientific or academic affairs. Duties will include international scientific relations and facility in at least one foreign language would be an advantage. Salary, according to age and experience in range £2,800 to £3,200 with superannuation and children's allowances.—Applications marked "Personal" stating age, present salary, previous experience and the names of two referees, to be sent to Sir Howard Florey, President, The Royal Society, Burlington House, London, W.1, before February 15, 1962.

EXPERIMENTAL OFFICER OR ASSISTant Experimental Officer required by Research Institute, Pirbright, for work on development of live virus vaccines. Qualifications: H.E.C. Biology or equivalent. Salary scale: Assistant Experimental Officer, £551 at age 20 rising to £98; or Experimental Officer, £1,087 rising to £1,33[illegible] starting salary dependent on age and experience. House available for married man.—Applications to Secretary.

APPLICATIONS ARE INVITED FROM honours graduates in chemistry or biochemistry to undertake physico-chemical research on abnormal serum components. Suitable for Ph.D. study.—Apply, with details of academic career to Dr. P. Johnson, Department of Colloid Science, Free School Lane, Cambridge.

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Applications are invited from persons qualified to pursue M.Sc. and Ph.D. work in chemistry for Teaching and Research Assistantships. Stipends are dependent on the number of hours per week given to teaching work. The maximum is 12 hours per week during the session October to May inclusive. The four summer months are devoted entirely to Research leading to the degree. The maximum stipend amounts to $2,800 for a twelve-month period.

Research opportunities are available in Analytical Chemistry, Inorganic Chemistry, Radiochemistry, Physical Chemistry, Colloid Chemistry, Immunochemistry, Organic Chemistry and the Chemistry of Cellulose and Lignin.

For further information please write to:
The Chairman,
Department of Chemistry,
McGill University,
Montreal, Quebec, Canada.

McGILL UNIVERSITY

POST-DOCTORAL APPOINTMENTS IN CHEMISTRY

Post-doctoral appointments are available for studies in:

(1) Atom reactions, chemiluminescence, mass spectrometry (with particular emphasis on upper atmosphere reactions).
(2) Nuclear and Radiochemistry, with particular emphasis on high and low energy nuclear fission.
(3) Physico-chemical aspects of Immunochemistry.
(4) Organic Chemistry of Wood and Cellulose.

Salary: Commensurate with qualifications and experience.

Applicants should submit official documents attesting to academic qualifications and at least two supporting letters to the Chairman, Department of Chemistry, McGill University, Montreal, Quebec, Canada.

UNIVERSITY OF QUEENSLAND

READER OR SENIOR LECTURER IN ELECTRICAL ENGINEERING

The University invites applications for the above-mentioned position. Applicants for the Readership are required to have a higher degree in electrical engineering and experience in some aspect of electronics or communications. Evidence should be submitted of experience of lecturing on theoretical topics to honours students and of ability to supervise and participate in research projects. For a Senior Lectureship applicants must hold an honours degree in electrical engineering with specialization in electronics. The salary range for Reader is £A.3,000 by £A.100 to £A.3,300 and for Senior Lecturer, £A.2,520 by £A.100 (4) by £A.80 (1) to £A.3,000. The successful applicant will be entitled to participate in the benefits available to the academic staff which include F.S.S.U. type superannuation, housing assistance, study leave and travel grants.

Additional information on the conditions of appointment, staffing and activities of the Department, together with application forms, will be supplied on request to the Secretary, Association of Universities of the British Commonwealth (Branch Office), Marlborough House, Pall Mall, London, S.W.1. Applications close in Brisbane and London on January 13, 1962.

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Applications would also be considered from persons of outstanding ability who wish to offer another specialist mechanical engineering subject in place of one of the above.

Applicants for the above post should hold a good degree or equivalent qualification, and have suitable industrial experience; good experience of research methods would be an advantage.

Salary Scales (from January 1, 1962):

Senior Lecturer, £1,845 to £2,060 per annum.

Anyone interested in the above post can obtain application forms and more information from the Clerk to the Governing Body, Town Hall, Hendon, London, N.W.4. Application forms should be returned within fourteen days of the appearance of this advertisement.

C. E. GURR, M.Sc., Ph.D.,
Chief Education Officer.

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Full particulars and forms of application may be obtained from the Head of the Department of Applied Physics, Lanchester College, Priory Street, Coventry.

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A course of eight postgraduate lectures on "Optical Methods in Combustion and Aerodynamics: The Optics of Flames" will be given by Dr. F. J. Weinberg in the Department of Chemical Engineering and Chemical Technology on Tuesdays at 2.15 p.m., commencing January 30, 1962.

Details from the Registrar.

GRANTS & SCHOLARSHIPS

McMASTER UNIVERSITY

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Applications are invited for Graduate Scholarships in the Department of Physics, McMaster University, from students qualified to register in courses leading to the M.Sc. and Ph.D. degrees. These scholarships may be supplemented by Departmental Assistantships, requiring ten hours per week service during the seven-month academic year, to provide a yearly income (less fees) of $2,400 to $2,600. Graduate Calendars and application forms for graduate study may be obtained from the Secretary of the Faculty of Graduate Studies.

Further information concerning the types of research in progress and application forms for scholarships may be obtained from Professor M. W. Johns, Chairman, Department of Physics, McMaster University, Hamilton, Ontario, Canada.

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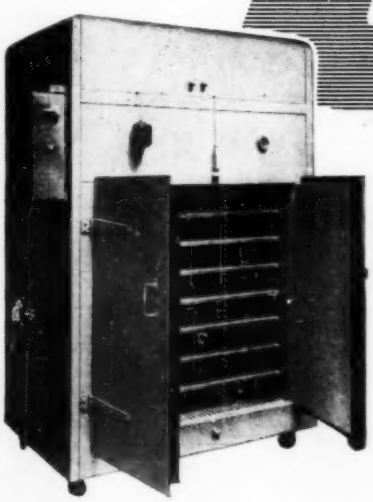

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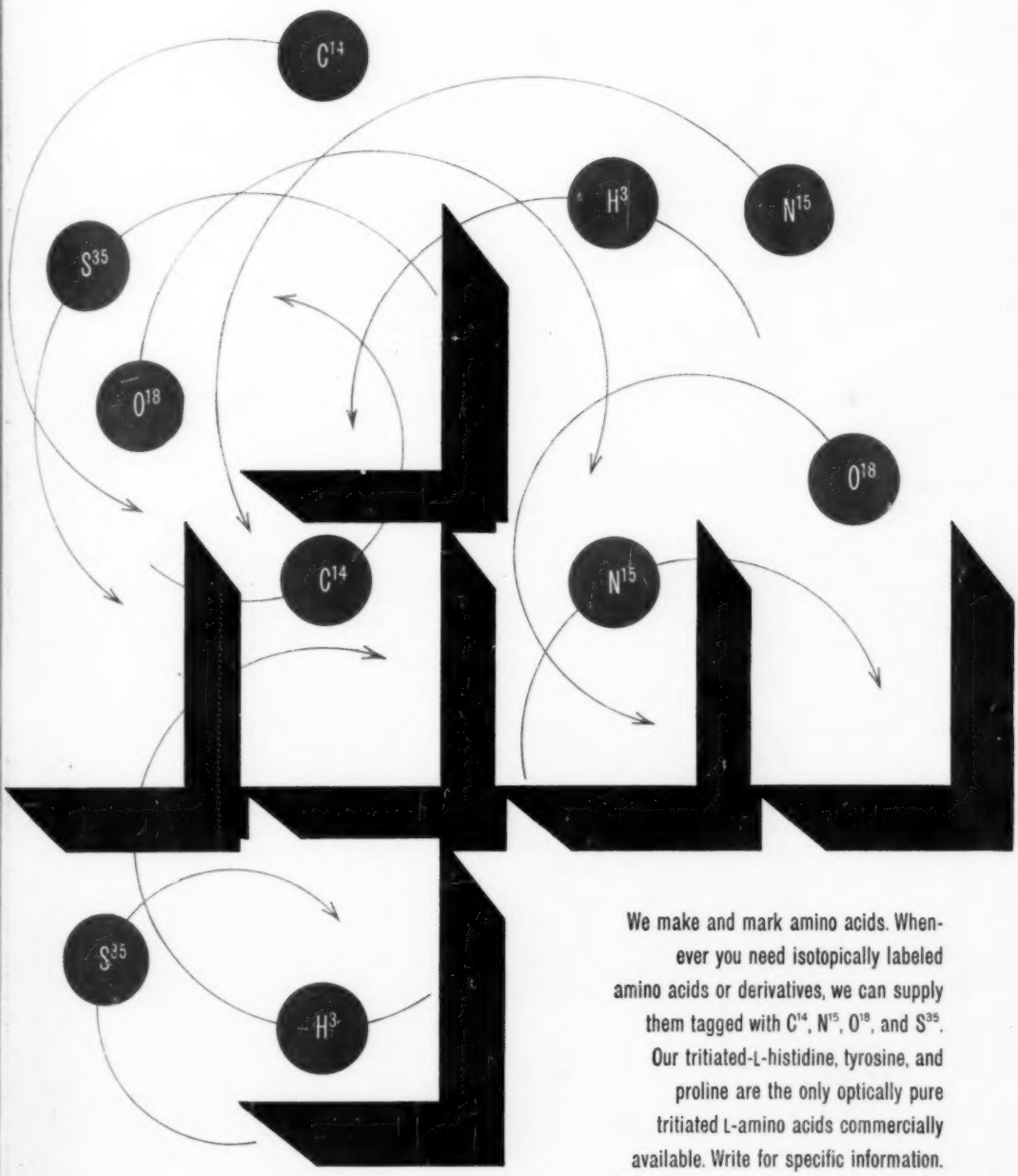

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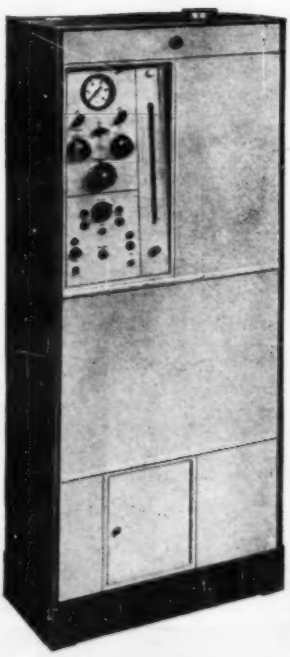

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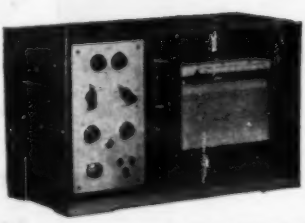

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XUM